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THE HEART AND THE AORTA IN EARLY SYPHILIS

CLINICAL OBSERVATIONS *

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AND
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BOSTON

INTRODUCTION

The organism of syphilis invades the blood stream early in the infection, and it is generally admitted that during this period of invasion the treponemes lodge in the various viscera, including the heart and the aorta. Then follows a considerable latent period, after which symptoms and signs of syphilitic heart and aortic disease may become manifest, usually a number of years after the original infection.

Recently, however, there have been several reports emphasizing that signs of involvement of the heart and aorta in syphilis appear in the early stages of the disease. This is logical in view of the known facts pertaining to syphilitic infection, but is not well borne out in the clinical experience of many observers. Because we have felt that many of the reported cases have not been critically enough examined, we undertook the investigation described in this report.

LITERATURE

Grassman's [1] work is quoted in most articles on cardiac syphilis. In 288 cases of secondary syphilis he detected arrhythmias or pulse disturbances in 85 per cent, and murmurs in 40 per cent.

Amelung and Sternberg [2] in 1924 reported that they believed Grassman's figures were too high. They had followed 275 cases in the early stages for one year. Twenty-one per cent showed either cardiac enlargement (checked by roentgen-ray examination), altered quality of the second sound, tachycardia, extrasystoles or murmurs. One case showed an aortic regurgitation labelled by the authors as definitely syphilitic.

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* From the South Medical and Cardiac Clinics, Cardiographic Laboratory and X-Ray Department of the Massachusetts General Hospital.

1. Grassman, K.: Deutsches Arch. f. klin. Med. **68**:455, 1900; ibid. **69**:58 and 264, 1901.

2. Amelung, W., and Sternberg, A.: Arch. f. klin. Med. **145**:34 (Sept.) 1924.

Brooks [3] reported that of 300 cases of syphilitic heart disease twenty-four (8 per cent) showed cardiac involvement in the secondary stage.

3. Brooks, Harlow: Am. J. Syph. **5**:217 (April) 1921.

Two of these were proved by postmortem examination. Brooks [4] has also reported two cases of aortic aneurysm developing within six months of the primary lesion. He regards tachycardia, extrasystoles, precordial pain, palpitation, dyspnea, apical systolic murmurs, cyanosis, and a state of apprehension as indicative of the possibility of heart damage in the early stages. The most frequent pathologic lesions consisted in perivascular infiltrations around the coronary arteries and their branches resulting in myocardial damage. Brooks believes that involvement of the heart may be noted early and may end fatally or may remain long quiescent.

Moore [5] agrees with Brooks in believing that the heart may early show signs of involvement. He reports a case of a male, aged 24, with a positive Wassermann reaction and a beginning macular rash, who had had precordial pain for a few days. His temperature was 99.6 degrees and the pulse was 110. There was a slightly enlarged area of cardiac dulness, an occasional extrasystole, and a soft systolic murmur at the base. With antisyphilitic therapy the symptoms subsided.

Hazen [6] states that myocardial disturbances may occur. He quotes a case that developed a serious myocarditis before the secondary stage. According to Hazen, if myocarditis develops during the secondary stage, "the principal features are arrhythmia, particularly intermittance and tachycardia, and at times extrasystoles. . . . The irregularity becomes more marked after mild exercise or through nervous fear. Precordial pain is not common, and various writers disagree as to the amount of dyspnea present. Cyanosis frequently occurs."

Engman [7] believes that myocarditis, valvular disease, and aortitis begin during the early invasive stage, although there may be no symptoms until later. Acute symptoms, such as arrhythmia and precordial pain, occur during the primary and secondary periods but are of short duration. Subacute aortitis is not uncommon.

Wiltshire [8] says that cardiac arrhythmia is often noted in the secondary stage, but that the pericardium and endocardium are rarely affected.

Liek [9] reports a case of aortic dilatation interpreted by roentgen-ray examination developing seven months after the primary lesion.

Howard [10] states that of fifty syphilitic patients in the secondary stage, eight complained of palpitation, five of cardiac pain, and three of dyspnea. One had edema. Cardiac dilatation may often be made out,

4. Brooks, Harlow: Am. J. M. Sc. **146**:513, 1913.
5. Moore, W. C.: Am. J. M. Sc. **160**:660 (May) 1918.
6. Hazen, H. H.: Syphilis, 1921, p. 205.
7. Engman, M. F.: Nelson's Loose-Leaf System of Medicine **2**:290.
8. Wiltshire, H.: Tr. West London Med.-Chir. Soc., 1922.
9. Liek: Fortschr. a. d. Geb. d. Röntgenstrahlen **17**:23, 1911.
10. Howard, T.: Am. J. M. Sc. **167**:266 (Feb.) 1924.

Howard says, together with occasional extrasystoles and frequently a reduplicated second sound at the apex. A case is cited of a man, aged 20, who had a primary lesion three months before coming under observation. On admission he had had palpitation and precordial pain for from six to eight weeks. There was an apical systolic murmur. The right border of dulness was 3 cm. from the midsternum; the left border of dulness was 17 cm. from the midsternum and in the anterior axillary line. The second sound was reduplicated at the apex. Rest and mercury cured the symptoms in one month, and the transverse diameter of the heart decreased from 20 to 15 cm.

Boyd,[11] in a review of 4,000 necropsies, found a beginning aneurysm in a case with primary syphilis.

Oddo and Mattei[12] quote Fournier as finding disturbances of the heart rhythm frequently in cases of secondary syphilis. According to these authors, cardiac syphilis in the secondary stage of the disease is not infrequently fatal. They recognize two classes of patients with heart lesions in secondary syphilis: those with the "benign" arrhythmias, and those in whom the cardiac syphilis takes a "malignant" form with rapid decompensation and ultimate death. A case is cited as of pericarditis due to syphilis in the secondary stage that was obviously a case of coronary thrombosis—from the standpoint of history, course, physical and postmortem findings.

Bonnin[13] states that Etienne had seen cases of syphilitic aortitis appearing nine, eight, and even three months after the chancre. Symptoms of aortitis are, however, according to Bonnin, rare in the first year of the infection.

Vaquez[14] cites a case that he had seen in a girl of 20 with secondary syphilis who developed a permanently slow pulse with Adams-Stokes' attacks, presumably on a syphilitic basis.

Not all observers, however, believe that evidence of cardiac damage is common in the early stages of syphilis. Cohn[15] says that "syphilis rarely causes detectable damage to the heart in the primary and secondary stages."

Wilson, Wile, Wishart and Herrmann,[16] at the conclusion of a report concerning the electrocardiographic changes following arsphenamine treatment of cardiac and aortic syphilis, state, "In twenty patients with primary and secondary lues intensive arsphenamine treatment produced no electrocardiographic abnormalities. A study of about sixty

11. Boyd, L. J.: Am. J. M. Sc. **168**:654 (Nov.) 1924.
12. Oddo, C., and Mattei, C.: Arch. d. mal. d. cœur **13**:289 (July) 1920.
13. Bonnin, H.: Medecine **7**:156, 1925.
14. Vaquez, H.: Diseases of the Heart, 1924, p. 319.
15. Cohn, A. E.: Nelson's Loose-Leaf System of Medicine **4**:333.
16. Wilson, F. N.; Wile, U. J.; Wishart, S. W., and Herrmann, G. R.: Proc. Soc. Exper. Biol. & Med. **23**:275, 1926.

patients with primary and secondary lues has convinced us that reliable clinical or electrocardiographic evidence of involvement of the heart or aorta during this stage of the disease is decidedly rare."

Marvin,[17] who in 1920 began an investigation at the Massachusetts General Hospital similar to ours, reports that he saw thirty-six patients with a primary lesion of several weeks' duration or early secondary manifestations. The number of visits made by each patient did not exceed five in any case and in most instances was less than that. Each patient was examined at each visit as to the size of the heart, rhythm, murmurs, cyanosis and so on, and was questioned as to the occurrence of any symptoms. Several patients with asymptomatic rheumatic heart disease were excluded. The results were absolutely negative. There were no symptoms, murmurs or irregularities. Although one patient had occasional auricular premature beats, it was found that they had been noted on an earlier medical record before the patient had acquired the syphilitic infection.

PRESENT OBSERVATIONS

Selection of Cases.—The basis for the present report is a series of fifty cases of primary and early secondary syphilis seen in the South Medical Department of the Massachusetts General Hospital in the spring of 1926. These cases were studied by means of a complete cardiac history and a thorough physical examination of the heart, supplemented in every instance by roentgen-ray and electrocardiographic study.

Considerable care was used in the selection of cases. It was felt that some of the confusion in the past had resulted from lack of care in excluding other forms of heart disease—for example, rheumatism or arteriosclerosis—in the patients studied, and from ascribing the signs and symptoms found to the syphilitic infection. Six patients were discovered with mitral stenosis presumably of rheumatic origin, and these were excluded from our series. Five of these six cases had an accompanying mitral regurgitation, and two had in addition an aortic regurgitation, in all cases asymptomatic.

No patients over 40 years of age were included in the series. This selection was for the purpose of preventing so far as possible the complications of coronary sclerosis. While realizing that no age limit artificially set is of absolute value, we felt that this form of selection would aid materially in ruling out this complication. In addition each case was examined to determine the condition of the radial and brachial artery walls and the retinal vessels. No cases of arteriosclerosis in these localities were found. There was no arcus senilis present in any

17. Marvin, H. M.: Personal communication to the authors.

case. We were prepared to exclude any cases of essential hypertension but none were found.

Because we realized the rôle played by the cardiac neuroses in the symptomatology of the cardiovascular apparatus, an estimate was made in each case of the mental attitude of the patient, but no cases of true neurosis were discovered. One patient with an enlarged thyroid and associated cardiac symptoms was excluded from the series.

Finally, an effort was made to exclude all cases complicated by other conditions than syphilis. The most frequent complications found were gonorrhea and pregnancy. In other words, the series was made to include so far as possible cases with a syphilitic infection only. Nevertheless, there are included in the fifty, one patient with a mild diabetes, one with gonorrhea, one with tuberculosis, and one pregnant woman. These four cases gave an absolutely negative cardiovascular study.[18]

Age, Sex, Race and Occupation.—There were nineteen females and thirty-one males in this series. The ages varied from 16 to 34 years. The age distribution is given in table 1.

TABLE 1.—*Age Distribution in Fifty Cases*

Age	Cases	Age	Cases	Age	Cases
16 years	1	22 years	3	29 years	3
17 years	2	23 years	5	30 years	1
18 years	3	25 years	4	31 years	3
19 years	2	26 years	3	32 years	3
20 years	2	27 years	2	34 years	3
21 years	9	28 years	1		

Forty-seven of the patients were white and three were colored. Thirty-four of the white patients were born in the United States. Five patients were Italian; one was Scotch; one Irish, one Armenian, one Finnish, one Swiss, two Swedish, and one Russian.

The occupations showed the usual variations.

Family History of Cardiovascular Disease.—In seven cases there was a history of cardiovascular disease in the family. In five instances death came in middle or advanced age from "shocks" or "heart failure." The remaining two patients were sisters of the patients who died in the twenties of "heart disease," probably rheumatic.

Past History.—The incidence of rheumatic fever, chorea, tonsillitis, scarlet fever and diphtheria was recorded in each case. Twenty-one patients gave a positive history. Of these, eleven had had tonsillitis or frequent sore throats alone. Three had had scarlet fever alone. Two

18. It is of interest to note that in twenty-three congenital syphilitic infants and children under the age of 5 years who came to necropsy at the Massachusetts General hospital during the last fifteen years no macroscopic evidence of syphilitic involvement of heart or aorta was noted.

gave a history of diphtheria alone and one of these was questionable. An additional one had had diphtheria and occasional severe sore throats. One patient gave a history of scarlet fever, diphtheria and a tonsillectomy. In one instance there was a questionable attack of rheumatic fever ten years before. Two patients had had diphtheria with a questionable rheumatic infection.

Only five patients had experienced any possible cardiac symptoms prior to the present illness, and these were mild in nature. In one case there was moderate shortness of breath associated with a rapid gain of a large amount of weight since discharge from the army. Another patient complained of palpitation whenever she was nervous. One had had an "irregular heart" previous to a tonsillectomy eight years before at the age of 13, with no symptoms since the operation. Two patients gave a history of premature beats, in one case associated with short stabs of pain beneath the lower sternum.

Nineteen patients had passed life insurance or army examinations within a few years before the onset of the syphilitic infection.

Syphilitic Infection and Treatment.—Eleven patients were admitted with a primary lesion. Three had both the primary and early secondary manifestations, while thirty-six were admitted during the secondary stage of the disease.

It was impossible to state definitely the duration of the infection in seventeen patients. Four patients had entered promptly (i. e., a week or less) after discovering the primary lesion. Four others came in about two weeks after the appearance of the chancre. About a month elapsed before treatment was given in six cases. There was an interval of about two months in six cases, about three months in five cases, about four months in two, five or six months in two, eight months in one, two years in one, and in two cases several desultory injections by local physicians had been given over a period of six months to a year before intensive treatment was started at the Massachusetts General Hospital.

The duration of treatment is computed from the time the patient entered the South Medical Department to the time when he was seen by one of us. Only an approximation is possible because of the irregularity that characterizes the visits of certain patients. The duration of the treatment in the individual cases will be found in table 2, which also contains data for each case on the approximate duration of the infection before treatment, the probable duration of the infection when the patient was seen, and the amount of treatment that he had received.

The general plan of treatment for a patient appearing at the South Medical Department in the primary or early secondary stages of the infection may be broadly summarized as follows: Eight injections of an arsenical are given intravenously at weekly intervals unless signs

of toxicity from the arsenic supervene. If the patient is infectious an effort is made to have him enter the ward until the height of the infectivity is passed. While in the ward he receives arsenical injections every four days. After his discharge the treatment is the same as that outlined for the nonhospitalized patients. At the conclusion of the

TABLE 2.—*Summary of Cases*

Case	Stage on Entrance	Duration of Syphilis Before Entry	Duration of Treatment	Amount of Treatment: Injection of Arsenic	Amount of Treatment: Injection of Mercury or Bismuth	Total Duration of Infection When Seen
1	Secondary	1 mo.+	2 mos.	3	3	3 mos.+
2	Secondary	3 mos.?	3 mos.	8	5	6 mos.?
3	Secondary	6 mos.	7½ mos.	8	15	13½ mos.
4	Secondary	?	9½ mos.	8 + 4	15 + 2	9½ mos.+
5	Secondary	2 mos.+	2 wks.	3	0	2½ mos.+
6	Secondary	2 mos.	10 mos.	8 + 6	15 + 3	1 yr.
7	Secondary	?	1 wk.	2	0	1 wk.+
8	Secondary	3½ wks.	4¾ mos.	8	12	5½ mos.
9	Secondary	2 yrs.	11 mos.	8	12	2 11/12 yrs.
10	Secondary	1 mo.+	4 wks.	4	0	2 mos.+
11	Secondary	?	1 yr.	10 + 4	14 + 3	1 yr.+
12	Secondary	4 mos.	2 mos.	4	4	6 mos.
13	Secondary	2 mos.	1 mo.	5	0	3 mos.
14	Secondary	3 mos.	3 mos.	8	5	6 mos.
15	Secondary	2 mos.	1 wk.	1	0	2 mos.+
16	Secondary	?	8 mos.	8 + 8	7 + 9	8 mos.+
17	Secondary	?	2 mos.	9	0	2 mos.+
18	Secondary	1 yr.	1 mo.	5	0	13 mos.
19	Secondary	?	1½ mos.	6	0	1½ mos.+
20	Secondary	?	1 wk.	3	0	1 wk.+
21	Primary and secondary	?	5½ mos.	8	14	5½ mos.+
22	Secondary	?	3 mos.	8	8	3 mos.+
23	Secondary	?	2 wks.	3	0	2 wks.+
24	Primary	3 wks.	1 wk.	2	0	1 mo.
25	Secondary	5 mos.	1 wk.	2	0	5¼ mos.
26	Secondary	1 mo.	6 mos.	8	15	7 mos.
27	Primary	5 days	9 mos.	8	21	9 mos.
28	Secondary	6 mos.	6 mos.	8	8	12 mos.
29	Primary	days	3½ mos.	8	8	3½ mos.+
30	Secondary	2 mos.	1½ mos.	3	2	3½ mos.
31	Primary	3 wks.	2½ mos.	8	4	3¼ mos.
32	Primary	2 days	4¼ mos.	8	11	4¼ mos.
33	Secondary	?	5½ mos.	12	8	5½ mos.+
34	Secondary	?	3 mos.	3	11	3 mos.+
35	Secondary	?	1 wk.	3	0	1 wk.+
36	Secondary	3 mos.	4 mos.	8	11	7 mos.
37	Secondary	?	3 mos.	8	1	3 mos.+
38	Primary	2 wks.	2½ mos.	10	1	3 mos.
39	Primary and secondary	?	2 wks.	3	0	2 wks.+
40	Secondary	4 mos.	4 mos.	8	2	8 mos.
41	Secondary	3 mos.	3 days	1	0	3 mos.
42	Primary and secondary	days	1 mo.	6	0	1 mo.+
43	Secondary	7½ mos.	5½ mos.	8	7	13 mos.
44	Primary	2 wks.	1 mo.	7	0	1½ mos.
45	Secondary	1½ mos.	4½ mos.	8 + 8	4	6 mos.
46	Primary	2 wks.	1 mo.	6	0	1½ mos.
47	Secondary	1½ mos.	2½ mos.	8	0	4 mos.
48	Primary	2 wks.	10½ mos.	8 + 6	15 + 9	11 mos.
49	Primary	2 mos.+	6 mos.	8	12	8 mos.+
50	Primary	?	10 days	3	0	10 days+

course of arsenic therapy, fifteen intramuscular injections of mercury or bismuth are given at weekly intervals. After a rest period of six weeks the patient returns for a Wassermann test. If the test is positive the whole course of treatment is gone through again. If the test is negative six injections of an arsenical solution and ten or twelve of

the mercury or bismuth are given. From this point the treatment varies, but as no patient included in this series had received more than the amount outlined above, a further discussion is unnecessary.

Cardiac Symptoms Since Onset of Syphilis.—Two patients complained of occasional symptoms of palpitation probably due to extrasystoles, and in addition one of these patients at times had short stabs of pain beneath the lower sternum. In both patients these symptoms had been present for months before the acquired syphilitic infection. Another patient in answer to the routine questions stated that her feet and ankles were swollen at night, but on examination the heart was found to be in excellent condition and the local signs due to moderately developed varicose veins.

PHYSICAL EXAMINATION

The temperature was normal in all cases. As mentioned before no case showed an arcus senilis, and in all the eye-grounds were normal. No cases showed any abnormal pulsations, a tracheal tug, friction rubs, or evidence of congestive failure, including cyanosis and edema. The knee jerks and pupil reactions were likewise normal.

One of the most frequently reported signs of early cardiac involvement in syphilis stressed by certain authors is pulse irregularity. The pulse was regular in 39 of our cases. Nine other cases were regular except for sinus arrhythmia. Infrequent extrasystoles were found in two patients and in these cases the irregularity was not noticed by the patient. In neither of these cases were the premature beats present in the electrocardiographic tracings. The rate varied considerably. One patient showed a bradycardia of 50 that later mounted to 65 with the nervousness associated with having an electrocardiogram taken. There was no evidence of block in this case, and it probably represents a sinus bradycardia. Five cases had a rate of 60. Ten more had rates between 61 and 70. In twenty-three the rate was from 71 to 80. In seven the rate was from 81 to 90. And in two apprehensive subjects the rate ranged between 90 and 110. The form of the pulse was not remarkable, and in all cases the radial pulses were equal and synchronous. The radial and brachial artery walls were soft, and there was no capillary pulse.

In all cases the midclavicular line was used as the standard for the maximum left border of dulness and position of the apex impulse. In one case the left border of dulness to percussion was 1 cm. outside the midclavicular line. This case will be discussed later. With this one exception, the percussion outlines were normal.

The sounds were of good quality and normal in most cases. Two cases mentioned above under the consideration of the pulse showed rare

premature beats. A split pulmonic second sound was noted in two cases. Another case had a split first sound at the apex.

In three cases a soft transient systolic murmur was present at the apex. The murmur in these cases was markedly influenced by respiration and by change in position. It was never transmitted. In one other case a similar murmur was heard at the base of the heart. In the case mentioned above that showed the abnormal percussion dulness murmurs were found that will be described later.

The blood pressure findings were not important enough to summarize. There were no cases of hypertension. The highest pressure noted was 136 systolic, 80 diastolic. One third of the cases had systolic pressures between 100 and 110. Two cases gave systolic readings of 90 to 95.

LABORATORY EXAMINATIONS

Wassermann Test.—Either a Wassermann test or a dark field examination or both is made on each patient on entry. In only three cases of the series had no Wassermann test been made. It was positive in the last test at the time the patient was seen in thirty-three cases. In nine cases it had been positive but had become negative at the time the patient was seen. In five cases the Wassermann reaction had never been positive during the time the patient was receiving treatment. These were cases in which the diagnosis had been made by dark field examination on entrance, and in which the first course of treatment had not been completed.

Blood and Urine Tests.—These tests were not done on all patients. Blood counts and smears were made in only five, all of which were negative. Urine tests were made in twenty-three cases and were normal in twenty-one; one case showed some pus cells and the other, the diabetic case referred to early in the report, showed persistent traces of sugar.

Spinal Fluid Test.—The spinal fluid was examined in only one case. This spinal fluid gave a positive Wassermann reaction which eventually became negative under treatment.

ROENTGEN-RAY EXAMINATIONS

Teleoroentgenogram heart plates were taken of all patients. The roentgen-ray report was completely negative in thirty-one cases. One case that will be discussed later was slightly abnormal. In two patients, both short, obese persons, a high diaphragm caused a relative increase in the transverse diameter of the heart. In two cases the aortic pulsations as seen by the fluoroscope were slightly more prominent than usual. Four cases were described as having very slight prominence in the region of the auricles, but the cardiac measurements were within normal limits and no cardiac lesion was supposedly present. Three

cases were described as having a slightly prominent left ventricle, with measurements within normal limits. In five cases the notation was made that the transverse measurements of the heart were slightly beyond the maximum normal. This is assuming a standard of half the intrathoracic diameter for the maximum normal transverse measurement. According to Smith and Bloedorn,[19] the normal standard for the maximum cardiothoracic ratio is 57 per cent. All these five cases showed measurements exceeding only very slightly 50 per cent of the intrathoracic diameter, and in no case was this figure as high as 57 per cent. Another patient was described as having slight enlargement of the cardiac shadow downward and to the left as well as slight prominence of the right auricle. The last observation is very questionable, and the transverse diameter of the heart was 12 cm. in a chest of 23.5 cm. The final patient was described as having a slightly prominent left auricle and pulmonary artery, but in this case a slight thoracic rotation to the right rendered too rigid an interpretation of the shadow impossible.

ELECTROCARDIOGRAMS

The electrocardiographic tracings were completely negative in thirty-five cases except for some sinus arrhythmia and somatic tremor in certain ones of this group. The other sixteen cases also were normal, but exhibited certain slight and unimportant variations. Two cases had sino-auricular tachycardia with rates around 120 per minute. One of these cases and four other cases showed questionable or slight abnormal right axis deviation. A pregnant woman showed slight abnormal left axis deviation. The other findings may be summarized as follows:

Case 9: Left axis deviation; index plus 16; angle minus 30 degrees; P_2 plus 4 mm.; P_3 plus 3 mm.
Case 12: P_2 plus 4 mm.
Case 15: P_2 plus 3 mm.
Case 22: P_2 plus 3 mm.
Case 45: Very high Q-R-S in leads II and III.
Case 47: Normal rhythm; rate 52; P-R interval 0.18 seconds; somatic tremor; sino-auricular bradycardia.
Case 48: Questionable variation of the sino-auricular pacemaker.
Case 49: P_2 plus 3 mm.; T_2 plus 8 mm.

COMMENT

Forty-nine of the fifty cases in this series were normal or exhibited minor variations, principally in the roentgen-ray examination or electrocardiogram, which could not be ascribed to any pathologic process. It should be pointed out that all of these slight abnormalities may occur in persons who are perfectly normal in every other way. The burden of the proof must rest on those who would give a syphilitic basis for their interpretation.

19. Smith, H. W., and Bloedorn, W. A.: U. S. Nav. M. Bull. **16**:219 (Feb.) 1922.

The one case that may be regarded as possibly pathologic may be summarized as follows:

CASE 3.—A man, an Italian grocery clerk, aged 23, entered the South Medical Department, June 25, 1925. He gave a history of having had a penile sore in January, 1925. At entrance he showed a scar on the frenum, alopecia, generalized adenopathy, a macular rash, and mucous patches in the throat. The duration of the secondary manifestations was not ascertained. Treatment was immediately instituted and by the time he was seen by one of us, Feb. 16, 1926, he had received eight injections of arsphenamine, and fifteen intramuscular injections of mercurial oil and bismuth quinine iodide. His Wassermann reaction was strongly positive at the time of entrance but had become negative six months later.* A single urine examination four months after the treatment was started was negative. His family and past histories were negative from a cardiovascular standpoint. He had had no cardiac symptoms since the onset of the syphilitic infection.

The temperature was normal. There was no cyanosis or edema. The pupils reacted normally and the knee jerks were equal and active. The eyegrounds were negative. The artery walls were soft. The pulse rate was 80, regular, equal and synchronous, and rather full. There were no thrills, or abnormal pulsations and no tracheal tug. The apex impulse was in the fifth left interspace 9 cm. from the midsternal line. The midclavicular line was 8 cm. The left border of dulness was 9.5 cm. to the left of the midsternal line, the right border of dulness 3.5 cm. The dulness in the second space was 6 cm. wide. When examined in the sitting position there was no Broadbent's sign. The heart sounds were normal at the apex. The rhythm was regular and the rate about 80-90. There were no murmurs at the apex, but a slight systolic murmur was heard in the pulmonic area. No important change occurred in the recumbent position. After exercise and while he was recumbent the pulmonic systolic murmur was slightly increased but still was not loud. A short apical systolic murmur appeared. No diastolic murmurs were present. The heart shifted well with changes in position.

The electrocardiogram showed normal rhythm with a rate of 90. The roentgen-ray report was: The heart shadow was definitely increased in all diameters. The greatest prominence was to the left in the region of the left ventricle. There also was some prominence of the pulmonary arteries. Supracardiac dulness was increased but this was probably due to the dilatation of the pulmonary arteries. In the oblique view the shadow of the aorta appeared normal. There was slight general enlargement of the heart. The measurements were: right, 4 cm.; left, 10.1 cm.; transverse, 14.1 cm.; longitudinal, 15.5 base, 12.2 cm.; great vessels, 6.9 cm.; chest, 26 cm. There appeared to be a slight thoracic rotation in the roentgen-ray examination that might account for the small variation between the percussion measurements and those of the roentgenogram, as well as for the prominence in the region of the pulmonary artery. The cardiothoracic ratio was 54 per cent, or well within Smith and Bloedorn's normal limits.

We do not believe that this case can justly be labelled syphilitic heart disease on the basis of the slight and unimportant abnormalities exhibited.

SUMMARY AND CONCLUSIONS

A careful study of fifty cases of early syphilis at the Massachusetts General Hospital by history, physical examination, roentgen-ray examination and electrocardiogram showed no definite clinical evidence of disease of the heart or aorta in any case. A study of the literature shows that clinical evidence of cardiovascular disease in early syphilis is rare.

ALTERATIONS IN THE PERMEABILITY OF SKIN CAPILLARIES DURING PREGNANCY AND PUERPERIUM *

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AND
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Pregnancy and parturition offer an interesting field of observation, quite apart from purely obstetric considerations, because of the pronounced differences that occur in resistance to certain infectious diseases as well as other clinical conditions during the period of gestation and the puerperium. The change in the resistance to tuberculosis illustrates this very well.

That menstruation in itself is detrimental in tuberculosis is well known. The statement that the tuberculous woman "is killed by her menstruation" has often been repeated, and while mere repetition by no means carries conviction, there seems little doubt that careful clinical observation gives a firm basis for the belief. The biologic changes of the menstrual cycle, endocrine in origin, involve a profound alteration of the autonomic status of the organism and are associated, seemingly, with a definite ionic rearrangement. These metabolic changes are likewise associated with an increase in permeability of the vascular endothelium (observed in the meninges by Heilig and Hoff,[1] by Benda,[2] and by us in the capillaries of the skin.[3]

Pregnancy, the concensus of opinion would indicate, does not involve the necessary activation of a quiescent tuberculous focus. But in a certain number of cases there seems to be an increase in the lability of the lesions. This may be due to the increase in the enzyme content of the tissues and plasma, an increase that is only partially balanced by a simultaneous increase in antiferment.[4]

Parturition, without doubt, is injurious. Is it the physical effort, or is it the general biologic alteration of the organism associated with such changes as the involution of the uterus, or the beginning of lactation,

* From the departments of pathology and gynecology, University of Illinois College of Medicine.

1. Heilig, R., and Hoff, H.: Klin. Wchnschr. **3**:2049 (Nov. 4) 1924.
2. Benda, Robert: München. med. Wchnschr. **72**:1686 (Oct. 2) 1925.
3. Petersen, W. F., and Milles, George: The Relation of Menstruation to the Permeability of the Skin Capillaries and the Autonomic Tonus of the Skin Vessels, Arch. Int. Med. **38**:730 (Dec.) 1926.
4. Petersen, W. F.: Resistance to Tuberculosis, Arch. Int. Med. **21**:14 (Jan.) 1918.

that influences the resistance to tuberculosis so unfavorably? During involution proteolytic enzymes are swept into the circulation in quantity, at a time when the antiproteolytic property of the plasma diminishes. While the calcium balance has been studied, the results are conflicting and as practically all the work has been done without reference to the potassium metabolism, the results are of relatively little use to us.

In the observations here recorded we have made use of the simple blister method described elsewhere in this series of articles.[5] We have made observations on about 100 women, most of them normal term or postpartum cases. The details have been recorded in tables 1 to 5.

CHART 1.—*White Women, Antepartum*

Number	Race	Age	Parity	Clinical Diagnosis	Albumin	Blood Pressure	Blister Time in Hours	Serum Protein, per Cent	Blister Protein, per Cent	Ratio B/S	R/T
30	W	35	i	Term—with mechanical ileus; induced labor; spontaneous delivery (repeated tonsillitis, tonsillectomy, appendectomy, cholecystectomy)	—	110/68	8	7.10	4.58	0.64	8.0
31	W	22	viii	Antepartum (has had scarlet fever, rheumatism, pneumonia, tonsillectomy)	—	115/70	?	8.06	5.49	0.68	....
32	W	30	v	Term	..	.....	4½	8.06	5.50	0.68	15.0
33	W	35	viii	Term	—	125/80	9	7.63	5.29	0.69	7.6
34	W	18	i	Term	—	118/80	5½	7.76	5.40	0.69	12.5
35	W	..	viii	Term	—	142/92	5	7.34	5.09	0.69	14.0
36	W	24	i	Term	—	112/60	11	8.26	5.80	0.70	6.3
37	W	19	i	Seventh month	..	.....	8	8.00	5.80	0.72	9.0
38	W	28	ii	Term	..	.....	5½	7.00	5.04	0.72	13.0
39	W	25	ii	Term	..	.....	5	8.07	5.90	0.73	14.6
40	W	35	iv	Term	..	.....	6	8.06	6.06	0.75	12.5
41	W	19	i	Term	—	120/80	?	7.20	5.50	0.76	....
42	W	23	i	Eighth month	..	.....	5	7.05	5.49	0.78	15.6
42b	W	23	i	Term	..	.....	6	6.22	4.89	0.78	13.0
43	W	20	..	Eighth month (casts)	+	165/98	?	7.63	6.10	0.80	....
44	W	31	v	Third month; hematemesis	..	.....	5½	7.20	5.90	0.82	15.0
Average										0.725	

COMMENT

Including all cases the antepartum group has an average permeability ratio of 70.7, with practically no differences between the white and colored groups. The ratio for the postpartum group is 73.6.

A difference in the rate of blister formation seems to exist between the white and colored groups after parturition, the average time of blister formation for the white women being five and one-half hours, for the colored seven hours. As the majority of these observations had, of necessity, to be made by nurses busy with routine work, we are unable to place much reliance on the accuracy of these records.

5. Petersen, W. F., and Willis, D. A.: Capillary Permeability and the Inflammatory Index of the Skin in the Normal Person as Determined by the Blister, Arch. Int. Med. **38**:663 (Nov.) 1926.

CHART 2.—*Colored Women, Antepartum*

Number	Race	Age	Parity	Clinical Diagnosis	Albumin	Blood Pressure	Blister Time in Hours	Serum Protein, per Cent	Blister Protein, per Cent	Ratio B/S	R/T
45	C	18	i	Ninth month	—	118/78	5	7.10	4.00	0.57	11.0
46	C	21	iv	Term	—	120/92	?	7.63	4.53	0.60	....
96	C	20	i	Term	—	130/90	?	7.85	4.89	0.62	....
47	C	24	i	During labor	—	110/70	6	7.76	5.00	0.64	10.6
48	C	33	iv	Term	—	110/70	?	8.06	5.57	0.69	....
49	C	15	i	Seventh month	..	.....	6½	6.98	4.89	0.70	10.7
50	C	29	iii	Term	..	100/60	?	8.26	6.00	0.72	....
51	C	21	..	Term	..	.....	5	7.63	5.49	0.72	14.4
52	C	18	i	In labor 24 hours	..	.....	8	7.30	5.29	0.72	9.0
53	C	19	i	Eighth month	..	.....	?	7.41	5.50	0.74	....
54	C	16	i	Term	..	.....	?	7.41	5.49	0.74	....
55	C	17	i	Term	..	115/70	?	7.20	5.40	0.75	....
56	C	21	iii	Term	..	.....	7	7.47	5.60	0.75	10.7
57	C	31	iii	Term	..	.....	5	7.05	5.29	0.75	15.0
58	C	25	ii	Term	..	.....	6	7.76	5.90	0.76	12.6
59	C	37	..	Abortion, third month	..	.....	10	7.16	5.50	0.76	7.6
60	C	20	i	Term	..	.....	6	7.15	5.54	0.77	13.0
61	C	25	i	Term (casts)	—	150/100	?	7.00	5.94	0.77	....
62	C	20	iv	Term	..	.....	5½	8.28	6.40	0.78	14.2
63	C	18	i	Term	..	.....	5	7.55	6.00	0.80	16.0
64	C	20	ii	Eighth month	—	110/70	10	6.76	5.41	0.80	8.0
65	C	30	..	Fifth month (threatened miscarriage)	..	.....	5¼	6.70	5.35	0.80	15.2
				Average						0.70	

CHART 3.—*White Women, Postpartum*

Number	Race	Age	Parity	Clinical Diagnosis	Albumin	Blood Pressure	Blister Time in Hours	Serum Protein, per Cent	Blister Protein, per Cent	Ratio B/S	R/T
1	W	28	v	Postpartum 1 day (during pregnancy, headaches, scotoma, edema of legs)	—	130/95	6	7.20	4.68	0.65	12.0
1B	W	22	iii	Postpartum 4 days	..	.....	7	8.28	5.69	0.68	9.7
2	W	22	iv	Normal postpartum	..	.....	8	6.47	4.40	0.69	8.6
2B	W	33	iii	Normal postpartum; postpartum 5 days	..	.....	8	7.85	5.40	0.70	8.7
3	W	23	ii	Normal postpartum	..	.....	6	8.28	5.70	0.70	11.6
3B	W	37	vi	Normal postpartum; postpartum 2 days	..	.....	7¼	6.55	4.57	0.70	9.7
4	W	35	vii	Normal postpartum	..	.....	6	6.98	4.99	0.71	12.0
4B	W	21	i	Normal postpartum; (twins) postpartum 2 days	..	.....	6¼	6.98	5.00	0.71	11.3
5	W	31	iii	Normal postpartum	..	.....	5¼	7.70	5.50	0.71	13.5
5B	W	26	vi	Seventh month pregnancy; postpartum 4 days	..	.....	8	7.20	5.20	0.72	9.0
6	W	18	i	Normal postpartum	..	.....	5½	7.30	5.29	0.72	13.0
7	W	31	iv	Normal postpartum	..	.....	6½	7.63	5.70	0.74	11.3
7B	W	18	i	Normal postpartum; postpartum 5 days	..	.....	7¼	7.20	5.35	0.74	10.2
8	W	30	iii	Normal postpartum; postpartum 5 days	..	.....	5½	7.20	5.60	0.77	10.8
9	W	35	viii	Normal postpartum; postpartum 5 days	..	.....	4	7.63	5.90	0.77	19.2
11	W	21	..	Postpartum, eclamptic	..	.....	?	6.72	5.30	0.78	....
11B	W	39	v	Postpartum 5 days	..	.....	5	7.50	6.00	0.80	16.0
12	W	19	i	Normal postpartum	..	108/68	5	7.00	5.80	0.83	16.6
13	W	29	iii	Normal postpartum	..	.....	4	6.56	5.49	0.83	20.7
14	W	23	iii	Postpartum; psychosis	..	.....	4	6.76	5.69	0.84	21.0
				Average						0.735	

Average permeability of all antepartum cases 70.7
Average permeability of all postpartum cases 73.6

CHART 4.—*Colored Women, Postpartum*

Number	Race	Age	Parity	Clinical Diagnosis	Blood Pressure	Blister Time in Hours	Serum Protein, per Cent	Blister Protein, per Cent	Ratio B/S	R/T
14B	C	20	i	Postpartum 9 days	.....	13	8.28	5.20	0.63	4.8
15	C	23	..	Postpartum (albumin and casts)	146/90	..	5.35	3.55	0.66	....
16	C	23	ii	Postpartum	.....	7½	8.49	5.80	0.68	9.0
17	C	26	v	Postpartum	.....	7½	7.85	5.50	0.70	9.3
18	C	31	ii	Portpartum	.....	8	5.70	5.70	0.70	8.7
19	C	28	iv	Postpartum	.....	6¾	7.41	5.10	0.70	10.3
20	C	21	i	Postpartum	.....	9¼	4.89	4.89	0.70	7.5
21	C	32	..	Postpartum	.....	8¼	7.74	5.50	0.71	8.6
21B	C	19	i	Postpartum 5 days	.....	5¼	8.60	6.10	0.71	13.5
22	C	18	i	Postpartum (twins) hypertension	.....	5	6.22	4.47	0.72	14.4
22B	C	30	iv	Postpartum 3 days	.....	6	7.85	5.70	0.72	12.0
22C	C	17	i	Postpartum 8 days	.....	7	7.77	5.69	0.73	10.4
23	C	16	i	Postpartum	.....	6¾	6.88	5.09	0.74	11.0
24	C	20	iii	Postpartum	.....	6½	7.34	5.43	0.74	11.4
25	C	25	ii	Postpartum	.....	8¾	7.41	5.50	0.74	8.4
25B	C	27	vii	Postpartum 4 days	.....	8	7.10	5.29	0.74	9.2
26	C	21	i	Postpartum	.....	7½	8.60	6.50	0.75	10.0
26B	C	20	iii	Postpartum 5 days	.....	7	7.85	5.80	0.75	10.7
10	C	16	i	Postpartum 5 days	.....	5	7.63	5.90	0.77	15.4
10B	C	19	i	Postpartum 5 days	.....	6	6.82	5.25	0.77	13.0
27	C	17	i	Postpartum	.....	4¾	6.90	5.39	0.78	16.4
27B	C	26	iv	Postpartum 8 days	.....	8	8.06	6.30	0.78	9.7
28	C	22	ii	Postpartum	.....	7	7.20	5.70	0.79	11.3
29	C	38	v	Postpartum; hypertension	.....	6	7.15	5.70	0.80	13.3
29B	C	19	iii	Postpartum 6 days	.....	8	7.85	6.50	0.82	10.2
29C	C	26	iii	Postpartum 1 day	.....	6	6.33	5.49	0.86	14.3
Average									0.737	

CHART 5.—*Permeability Ratio Before and After Delivery; Average Before 70.1, Average After 73*

Number	Race	Age	Parity	Clinical or Postmortem Diagnosis	Albumin	Blood Pressure	Blister Time in Hours	Serum Protein, per Cent	Blister Protein, per Cent	Ratio B/S	Ratio B/S Change
67	W	20	i	Antepartum	—	140/78	6½	7.85	5.37	0.68	
				Postpartum fourth day	..	.....	6	6.98	4.89	0.70	+0.02
68	C	19	i	Antepartum	—	120/80	?	7.52	5.20	0.69	
				Postpartum fifth day	—	.....	6	6.77	4.68	0.69	None
69	W	36	v	Antepartum	..	Normal	6½	7.70	5.29	0.70	
				Postpartum fourth day	..	.....	6	6.65	4.89	0.73	+0.03
70	C	18	i	Antepartum	—	110/80	?	7.63	5.49	0.72	+0.05
				Postpartum fourth day	..	.....	6	6.55	5.05	0.77	
71	W	27	i	Antepartum	—	128/86	6½	6.98	5.21	0.74	—0.02
				Postpartum fifth day	..	.....	8	7.20	5.20	0.72	
72	C	17	i	Antepartum	..	.....	6¼	6.55	5.00	0.76	+0.01
				Postpartum fourth day	..	Normal	8	6.55	5.09	0.77	
73	C	21	i	Antepartum	..	Normal	?	7.85	5.70	0.76	+0.02
				Postpartum fifth day	..	.....	6½	6.22	4.89	0.78	
74	W	20	i	Term: March 2	..	Normal	6	6.65	?	?	?
				March 16, postpartum 24 hours	..	Normal	8	7.63	5.23	0.68	
				April 2, puerperal infection (endometritis, streptococcus hemolysis)	+	.....	8	7.63	6.40	0.84	
75	W	35	i	Eight months pregnant, March 2	..	.....	7¼	8.49	5.69	0.67	+0.07
				April 2, seventh day postpartum (multiple fibroid)	..	.....	6½	6.98	5.20	0.74	
76	C	23	i	In labor 14 hours	..	.....	8	7.34	4.37	0.59	+0.15
				Postpartum 6 days	..	.....	6	8.06	5.90	0.74	

The observed differences in permeability can perhaps be shown more clearly in chart 1.

It will be observed that during labor the capillaries of the skin are less permeable, and that relatively more of the antepartum than postpartum cases are in the group of lowered permeability (59-69); above that the postpartum cases predominate. The pathologic cases predominate in the groups of greatest permeability.

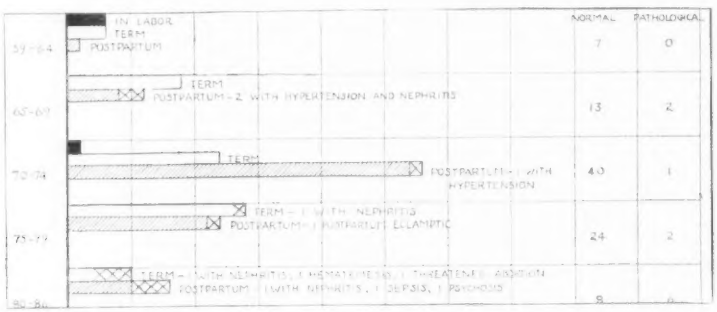

Chart 1.—Permeability ratio by groups: black columns, cases in labor; white columns, cases at term; shaded columns, cases postpartum, and crossed columns, pathologic cases.

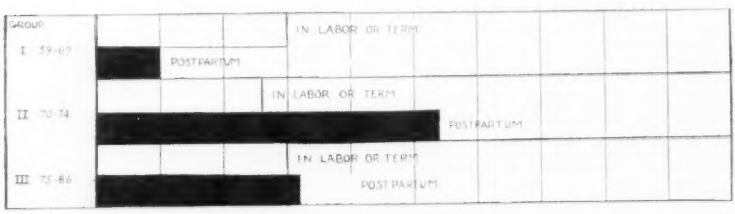

Chart 2.—Permeability ratio in groups of cases classified as (1) low permeability, (2) normal permeability and (3) high permeability (pathologic cases excluded: White columns, in labor or term; black columns, postpartum.

In chart 2 the pathologic cases have been eliminated and only three groups used: 1, relatively lowered permeability; 2, normal permeability; 3, increased permeability.

In surveying the tables it is interesting to note that the cases of hypertension with nephritis are to be found at the extremes of the range of permeability. In table 1 the single case of nephritis with moderate hypertension has a ratio of 0.77.

In table 2, two of the impermeable cases give a history of repeated infectious diseases, while at the permeable end is found a case of nephritis (blood pressure, 165) and one of hematemesis.

In table 3 the least permeable is a patient with toxemia during pregnancy, at the permeable end of the scale, an eclamptic case and a case of psychosis.

In table 4 one case of hypertension is found with a normal rate (72); the other two are at the opposite ends of the scale.

The change in permeability in such a condition as psychosis naturally brings up the question whether the increase in permeability results in the activation of a latent cerebral condition (in the nature of a focal reaction) or whether the development of the psychosis and the change in permeability are both merely coincident alterations based on some fundamental and underlying factor not determined.

We incline to the concept that we deal with a focal reaction. We find a similar condition in the development of an alcoholic psychosis. Long continued injury has here created an unstable cerebral condition and any disturbance associated with an increased vascular permeability (an infection, trauma, a nonspecific injection, an added alcoholic debauch) will initiate and make clinically manifest a disturbance in an area that has already been the seat of a subclinical pathologic alteration. We have developed the subject at some length elsewhere.[6]

Obviously, a similar relation pertains in relation to the tuberculous focus, the details of which we have already discussed in the article on menstruation.

In comparing the results of the study of the disappearance time of intradermally injected salt solution [7] with alterations in the capillary permeability in the normal and toxic pregnancies, a certain relationship is to be observed. In eclampsia, for instance, the disappearance time is markedly shortened and the capillary permeability increased. The shortening of the disappearance time has been interpreted as due to an increased affinity of the tissues for water.

Runge and Kessler [8] found that at the commencement of pregnancy there is a rise of osmotic pressure of the plasma colloids; this gradually falls after the fourth month, rises again suddenly during labor and again falls during the early days of the puerperium. The protein concentration of the plasma shows parallel changes, while the specific viscosity varies inversely. In the group of cases studied before and after delivery (table 5) the protein concentration at term was 7.436 per cent (ten cases) and 6.959 after delivery.

CONCLUSIONS

The capillary permeability of the skin during pregnancy averages 70.5 (forty-seven cases). During labor the permeability is reduced and the blister time increased (sympathetic tonus of the skin).

6. Petersen, W. F.: Am. Rev. Tuberc. **5**:218 (May) 1921.
7. Lash, A. F.: Surg. Gynec. Obst. **43**:40 (July) 1926.
8. Runge, H., and Kessler, R.: Arch .f. Gynäk. **127**, Sept. 9, 1925.

During the puerperium the average permeability is 73.6 (fifty-five cases).

Psychosis, hematemesis, threatened abortion, postpartum eclampsia and sepsis were associated with increased permeability. Hypertension and nephritis were either high or low in capillary permeability, except in one case.

THE PERMEABILITY OF THE SKIN CAPILLARIES IN VARIOUS CLINICAL CONDITIONS *

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In the preceding articles of this series [1] we have discussed in detail some of the factors that underlie alterations in capillary permeability. We have emphasized that the endothelial cell of the capillary wall, quite apart from any adventitious muscular elements, is as every cell possessed of the property of changing the state of the cell membrane, becoming either more or less permeable as the case may be. This change is associated by coincident changes in the caliber of the capillary, for the cell membrane that is permeable limits a cell that is softer and less rigid; such cells when forming a tube (as a capillary) will be more readily pushed and stretched by any force on the inside of the tube. This leads to the dilation of the capillary. Such changes in the cell membrane depend (*a*) on the hydrogen ion concentration of the tissues and fluids concerned; this in turn involves (*b*) changes in equilibrium of the other ions, changes which become most apparent and which are best understood from the study of alterations in the calcium and potassium ratio. But such ionic rearrangement is only one of the factors with which we must deal, although perhaps the most primitive and, therefore, the most important. We must consider, second, the control by the hormones, some of which make the cells more permeable (parathyroid, sex gland, perhaps thyroid), others of which (suprarenals, pituitary) have the opposite effect. These, too, may act directly on the cells, but probably are greatly modified in their activity by the ionic equilibrium existing at the cell membrane. Finally, they depend on the actual autonomic nervous apparatus, which we commonly think of in terms of sympathetic and parasympathetic systems. The actual reaction elicited by such stimulation depends again on the ionic equilibrium of the cell at the time the impulse reaches it. For the capillary wall this third mechanism is, I believe, of less importance than the other two. The mechanism does, however, directly control the rate of flow to the capillary by its influence on the arterioles. Probably some sympathetic fibers actually control capillary caliber in a limited way in regions in which adventitial elements

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1. Petersen, W. F., and Willis, D. A.: Capillary Permeability and the Inflammatory Index of the Skin in the Normal Person as Determined by the Blister, Arch. Int. Med. **38**:663 (Nov.) 1926. Petersen, W. F., and Milles, George: The Relation of Menstruation to the Permeability of the Skin Capillaries and the Autonomic Tonus of the Skin Vessels, ibid. **38**:730 (Dec.) 1926. Petersen, W. F., and Lash, A. F.: Alterations in the Permeability of Skin During Pregnancy and Puerperium, this issue, p. 12.

are well developed and constant in occurrence. We may with propriety speak of the vegetative control of the capillaries and to Kraus [2] and his school, as well as to the physiologist Ebbecke [3] we owe the greater part of the clarification that this particular field has undergone.

We should like to emphasize that while we speak of capillary permeability and have studied this particular phase of tissue activity in this series of articles, we recognize that the former is only an index of what is happening in the tissue in general.

We can trace much of the interest in the capillary and its importance in clinical phenomena to the work of Otfried Müller,[4] who has worked out many of the details of capillary microscopy.

From his laboratory, too, has come the suggestion that the ordinary cantharides blister might offer a useful method of approach to the problem of capillary, and tissue exchange and his associate Gänsslen [5] was the first to publish work dealing with a study of clinical conditions. He gave particular attention to the blister time and to the relative concentration of sugar and nonprotein nitrogen in blood and blister fluid.

Gänsslen applied six small plasters to the outer surface of the ankle and left these on for three, five, seven, nine, eleven and thirteen hours. The time of blister formation was then regarded as that time the plaster remained on the skin. His normal time was about twelve hours. This varied to some extent with different cantharides plasters employed and he also considered the possibility of seasonal variation. Gänsslen did not make a comparative study of the amount of blister protein and serum protein, although Müller in his introduction mentions the probability that such a study might be of interest. Gänsslen found a short blister time in the following conditions: vasoneuroses, urticaria, angioneurotic edema, dermographia, urticaria factitia; hemorrhagic diatheses (one-fourth and one-fifth the normal blister time), and severe clinical conditions such as pernicious anemia, myelogenous leukemia, icterus, sepsis; endocrine disturbances—hyperthyroidism, Raynaud's disease with pituitary disturbance; following roentgen-ray castration of women; in one case of glomerulonephritis. He determined a prolonged blister time in hypothyroidism, myxodema, diabetes and in the chronic nephritides.

Among the factors that must be considered which will bring about such an alteration in blister time will be the relative status of the tonus of the skin vessels. Other conditions disregarded for the moment, prolonged blister time will represent cases with increased sympathetic tonus, short blister time those with hyperparasympathetic tonus.

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2. Kraus, F., and Zondek, S. G.: Klin. Wchnschr. **3**:707 (April 22) 1924.

3. Ebbecke, U.: Jahresb. d. ges. Physiol., 1922, p. 233; Klin. Wchnschr. **2**:88, 112, 1923.

4. Müller, Otfried: Die Kapillaren der menschlichen Körperoberflache, Stuttgart, 1922.

5. Gänssler, M.: München. med. Wchnschr. **69**:263, 1922.

But in studying skin reactions we cannot assume that the relative tonus of the skin arterioles is a criterion for the tonus of the rest of the body. Müller and I[6] have demonstrated in a number of ways that there is a distinct antagonism between the status of the autonomic tonus of the peripheral as contrasted to the visceral regions. Consequently a sympathetic tonus of the skin vessels might be indicative of a parasympathetic status of the splanchnic area, and vice versa. We shall point out evidences of such conditions in the discussion of the clinical cases.

METHOD

The method that we have used differs from that of Gänsslen in that we have put on only one plaster, and that on the flexor surface of the forearm just below the elbow. This area is free from hair, the skin is of uniform thickness in men and women and the small bandage needed is not inconvenient for the patient. The plaster was left on for six hours (unless the blister formed in the interim), was then removed and the area watched carefully for the first sign of blister formation. This was then taken as the blister time. The plaster was always put on at the same time in the morning (4 a. m.), and a uniform strength and supply of cantharides plaster used throughout in the experiments. Protein determination was made by the refractometer, the blister fluid being calculated from the "exudate scale" of the Reiss table, while the serum reading was calculated from the "serum" scale. The serum sample was always obtained from the ear lobe at the time the blister was punctured. The ratio: $\frac{\text{blister protein}}{\text{serum protein}}$ is used as our permeability index. In addition we have indicated for each patient: $\frac{\text{permeability index}}{\text{time of blister formation}}$ to make apparent the modification of the permeability by the time of blister formation. The latter ratio may, in a measure, be regarded as an index of the inflammatory response of the skin and capillaries. We have in addition studied the amount of glycyltryptophan splitting enzyme present in blister and serum. This we have not tabulated for we have always found a much greater amount of enzyme in the blister fluid than in the serum. This has no necessary relation to the presence or absence of leukocytes in the blister fluid. The blister fluid should always be evacuated promptly when formed in sufficient amount. If left in the blister for any length of time the protein concentration begins to diminish, presumably because of proteolysis.

SKIN DISEASES

The skin cases, while small in number, offer several suggestive observations. The first case is that of a generalized dermatitis with a blister permeability of practically 100 per cent and prompt formation.

6. Müller, E. F., and Petersen, W. F.: Klin. Wchnschr. **5,** no. 2, 1926.

TABLE 1.—*Skin Cases*

Case	Sex*	Race	Age	Clinical or Postmortem Diagnosis	Albumin	Nonprotein Nitrogen	Blood Pressure	Hemoglobin	Red Blood Cells	Basal Metabolic Rate	Blister Time in Hours	Serum Protein, per Cent	Blister Protein, per Cent	Ratio B/S	R/T
27	♂	W	64	(1) Generalized dermatitis exfoliativa (fatal)	....	..	132/78	..	.....	....	2	5.00	4.90	0.98	40.0
				(2) Same, 3 weeks later	....	..	.....	..	.....	....	1.30	4.70	4.65	0.98	65.0
37	♂	W	23	Dermatitis herpetiformis (on arsenic)	....	40	.....	90	4,200,000	....	4	7.88	6.30	0.80	20.0
122	♀	W	20	Dermatitis herpetiformis and early tuberculosis right apex	....	38	.....	..	.....	....	5½	8.61	6.60	0.76	13.8
125	♀	W	21	Eczema	....	40	.....	..	.....	+16	3½	8.49	6.18	0.72	20.6
245	♂	W	59	Cellulitis of eye; diabetes; stricture posterior urethra; urticaria	++	58	.....	..	5,400,000	....	5	8.60	6.10	0.73	14.6
				Three weeks later, on treatment with calcium lactate, 15 grains three time a day, epinephrine chloride, 10 minims	....	..	.....	..	.....	....	10½	8.28	4.89	0.59	5.6

* In this column, ♂ indicates male; ♀, female.

This would indicate that the skin capillaries are not in a condition of stasis, but of active hyperemia with the arterioles parasympathetically oriented.

When we produce an active skin hyperemia (by means of ultraviolet irradiation) and wait until we have actual stasis (fourth day) with the surface red, hot and tender, a plaster will not produce a blister for a considerable period of time after one has been produced on the adjacent normal skin. Presumably the capillaries may here be permeable, but the arterioles are sympathetically oriented and in spasm.

Of the two cases of dermatitis herpetiformis, the one on arsenic is more permeable and has a shorter blister time than the second case. We have previously studied the rôle of arsenic on the capillary permeability.[7]

The effect of calcium lactate and epinephrine is well illustrated in case 245. From a permeability of 0.73 and inflammatory index of 14.6, the ratio is changed to 0.59 and inflammatory index 5.6.

As many of the problems of skin diseases and capillary permeability have been discussed very fully by Pulay [8] we shall not enter into the subject here.

CARDIORENAL CASES

We have grouped the cardiac and renal cases together, but have made subgroupings as noted in table 2. A large number of these cases have been observed at the county hospital, and it was not always possible to follow the individual cases to compensation or death to determine whether the disturbance was wholly cardiac or primarily renal. In the first group (*a*) are cases in complete decompensation of undoubted cardiac origin. In the second group (*b*) are decompensated or partially decompensated cases, as well as some practically recovered, of probable cardiac origin.

It will be noted that the permeability is very high in those with complete decompensation while in the second group a number have a normal permeability. The latter are cases in which arteriosclerosis was noted in the diagnosis or indicated by the relatively high blood pressure (cases 167 and 171) or had very little evidence of decompensation at the time the blisters were made (cases 19 and 39).

In the third group (*c*) have been collected cases primarily renal, but decompensated. Here, too, the permeability is very high. In the fourth group (*d*) are cases primarily renal or arteriosclerotic, all with some degree of decompensation.

7. Petersen, W. F., and Hughes, T. P.: J. Pharm. & Exper. Therap. **27**:411, 1926.

8. Pulay, E.: Ekzem und Urtikaria, Berlin, Urban and Schwartzenberg, 1925.

TABLE 2.—*Cardiorenal Cases* *

Case	Sex	Race	Age	Clinical or Postmortem Diagnosis	Albumin	Casts	Non-protein Nitrogen	Blood Pressure	Phenolsulphonphthalein, per Cent	Wassermann	Hemoglobin	Red Blood Cells	Blister Time in Hours	Serum Protein, per Cent	Blister Protein, per Cent	Ratio B/S	R/T
								A									
6	♂	W	39	O. H. D.; decompensation; Wassermann reaction +++	....	..	..	110/ 70	..	+++	..	.....	9½	7.09	6.20	0.87	9.1
232	♂	W	50	Mitral plus aortic lesions; decompensation; necropsy: valvular lesions; passive hyperemia; syphilitic aortitis; kidneys normal except for P. H.	+	+	46	160/ 50	..	+++	..	.....	3½	7.10	5.80	0.81	23.0
149	♂	W	18	A. S.; nephritis; O. H. D.; anasarca	++++	0	..	150/100	..	.....	..	.....	4½	6.12	5.00	0.81	18.0
161	♂	W	42	Chronic myocarditis; decompensation; asthma; P. H. lungs and liver; arthritis	+	..	..	156/110	..	.....	80	3,600,000	12	6.77	5.50	0.81	6.7
				Marked decompensation (cardiac origin). Average.....												0.82	
								B									
151	♂	C	46	O. H. D.; decompensation.....	..	..	..	140/ 60	..	.....	..	.....	8	6.90	6.00	0.87	11.0
23	♀	W	16	O. H. D.; myocarditis; endocarditis; incipient tuberculosis; tuberculous adenitis	..	..	..	105/ 45	..	.....	..	.....	4	8.06	6.60	0.82	20.5
142	♂	W	13	Valvular heart disease with beginning decompensation; no edema; chorea and arthritis	—	Occasional	..	108/ 70	..	.....	85	4,500,000	8	7.85	5.90	0.76	9.5
138	♂	W	60	Aortic and mitral lesions; myocarditis	+	..	..	135/ 58	..	+++	..	.....	24	7.20	5.39	0.74	3.0
211	♂	W	43	Mitral decompensation (some edema)	+	..	40	115/ 70	70	.....	..	.....	8½	6.77	4.80	0.70	8.2
19	♂	W	24	Valvular heart disease with beginning decompsensation; no edema	Trace	—	30	135/ 75	98	.....	80	4,600,000	5	6.87	1.79	0.69	14.0
39	♂	W	36	Valvular heart disease with edema	+	—	38	115/ 64	80	.....	70	4,650,000	4	7.45	5.21	0.69	17.0
167	♂	C	35	Myocarditis; decompensation; A. S.	+	..	..	132/ 76	..	.....	..	.....	12	7.20	4.89	0.68	5.6
171	♂	W	60	Mitral decompensation; emphysema	+	+	73	172/ 90	..	.....	..	.....	7	5.90	3.86	0.65	9.3
				Partial decompensation (cardiac). Average.....												0.73	
								C									
168	♂	W	90	A. S.; myocarditis; decompensation; senility	+	+	..	129/ 86	..	.....	..	.....	12	6.23	5.70	0.91	7.5
195	♂	W	51	A. S.; chronic nephritis; myocarditis; obesity; decompensation	—	—	..	170/110	..	.....	..	.....	5	6.88	5.50	0.81	16.2
163	♂	W	64	A. S.; myocarditis; chronic alcoholism; decompensation; senile dementia	—	—	..	170/ 60	..	+	..	.....	5	7.20	5.82	0.80	16.0
188	♂	W	68	Myocarditis (with edema).....	..	..	..	.....	..	.....	..	.....	8	7.74	5.90	0.76	9.5
				Marked decompensation (arteriosclerotic and renal). Average.....												0.82	

									D								
200	♂	W	37	Interstitial nephritis; myocarditis; decompensation	0	0	49	130/ 98	..	+++	..	.....	7½	6.77	5.30	0.78	14.0
242	♂	W	53	Myocarditis; decompensation	Trace	+	53	168/ 68	60	+++	..	.....	4½	6.55	5.15	0.77	17.0
124	♂	W	65	O. H. D.; chronic interstitial nephritis; cirrhosis	++	+	53	160/ 80	..	.....	..	.....	8	7.20	5.57	0.77	9.6
165	♂	W	67	A. S.; myocarditis; chronic arthritis; decompensation; P. H. liver	..	..	..	138/ 78	..	.....	..	.....	11	7.20	5.70	0.76	7.0
160	♂	W	60	Myocarditis; decompensation; P. H. liver and lungs	..	..	..	160/110	..	.....	..	.....	11	6.77	5.20	0.76	7.0
A264	♀	W	61	Chronic myocarditis with decompensation (tuberculosis anomalous right kidney ?)	+++	++	150	170/110	42	.....	83	4,300,000	6½	7.92	5.96	0.75	11.5
186	♂	W	63	A. S.; aneurysm; myocarditis; bronchitis	—	—	42	170/117	..	.....	..	.....	8	7.00	5.29	0.75	9.4
159	♂	W	56	O. H. D.; myocarditis; P. H.; A. S.; cholangeitis	..	..	..	.....	..	.....	..	.....	11	7.00	5.25	0.75	6.8
209	♂	W	37	Chronic interstitial nephritis; cardiac decompensation	+++	+++	..	195/110	..	.....	..	.....	8½	5.90	4.47	0.75	9.0
164	♂	W	62	Myocarditis; A. S.; decompensation; cholangeitis; P. H.	..	..	..	102/ 86	..	.....	..	.....	11	8.08	6.00	0.74	6.7
196	♂	W	42	Myocarditis; A. S.; decompensation	—	—	37	126/ 96	..	.....	..	.....	8	6.44	4.60	0.72	9.0
190	♂	W	66	Myocarditis; A. S.; decompensation	+	+	50	146/ 85	..	.....	..	.....	8½	6.83	4.89	0.71	8.3
231	♀	W	48	Nephritis; chronic myocarditis....	+	Occasional	29	118/ 80	58	.....	82	4,800,000	4½	8.10	5.29	0.65	14.0
189	♂	W	76	Chronic nephritis; decompensation	..	..	..	.....	..	.....	..	.....	11	6.66	4.37	0.65	6.0
				Partial decompensation (arteriosclerotic and renal).				Average.....								0.73	
									E								
33	♀	W	60	Chronic interstitial nephritis; tapeworm; mitral lesion	+ +	+ +	48	258/106	..	.....	..	.....	9	6.77	4.89	0.72	8.0
132	♂	W	55	Chronic interstitial nephritis; hypertension; cataract	+	+	57	218/120	..	.....	..	.....	7	7.95	5.70	0.71	10.0
2	♂	W	47	Chronic interstitial nephritis.....	+	+	36	235/130	55	.....	..	.....	10	9.55	5.85	0.61	6.1
114	♀	W	62	(1) Cerebral hemorrhage; (2) diabetes; necropsy: cerebro-arteriosclerosis with edema and hemorrhage; coronary thrombosis; cystopyelonephritis	+	+	68	120/ 70	..	.....	..	.....	13½	7.85	4.57	0.58	5.0
95	♀	W	53	Chronic interstitial nephritis.....	+	+	36	200/110	37½	.....	..	.....	6	9.65	5.50	0.57	9.5
				Arteriosclerotic and renal without decompensation.				Average.....								0.64	
									F								
264	♀	W	13	Chronic nephritis (pre-edematous stage) following scarlet fever and measles 7 years before	+++	++	116	190/138	5	.....	75	3,400,000	7	4.93	4.57	0.92	13.0
100	♂	W	28	Bilateral pyelitis	+	..	38	.....	..	.....	..	.....	6	7.76	5.50	0.70	11.6
192	♂	W	55	Myocarditis; decompensation; A. S.	..	..	..	.....	..	.....	..	.....	9	7.00	4.65	0.66	7.3
184	♂	W	65	Chronic myocarditis	..	..	..	.....	..	.....	..	.....	9	7.74	5.09	0.65	7.2
181	♂	C	35	Mitral lesion ?.....	..	..	..	.....	..	.....	..	.....	9½	9.11	5.90	0.64	6.7
76	♂	W	55	Pyelonephritis	..	..	..	132/ 86	..	.....	..	.....	5	8.70	5.39	0.62	12.4
152	♂	W	47	Decompensation; ascites (magnesium sulphate daily)	0	0	..	.....	..	.....	..	.....	8	6.55	4.00	0.61	7.6
				Miscellaneous. Average.....												0.00	

* In these tables, O. H. D. means organic heart disease; P. H., passive hyperemia, and A. S., arteriosclerosis.

In the fifth group (*e*) are the cases of hypertension and nephritis without decompensation. These cases have a low permeability and a relatively long blister time. The general capillary changes in nephritis associated with increased blood pressure have been studied in various

TABLE 3.—*Acute Infections*

Case	Sex	Race	Age	Clinical or Postmortem Diagnosis	Blood Pressure	Non-protein Nitrogen	Temperature	Blister Time in Hours	Serum Protein, per Cent	Blister Protein, per Cent	Ratio B/S	R/T
					A							
172	♂	C	37	Acute multiple arthritis	102/68	..	99.4	10	7.80	6.00	0.77	7.7
198	♂	C	30	Acute arthritis	.....	..	101	6	7.52	5.50	0.78	13.0
148	♂	W	35	Arthritis	130/60	..	98	10	8.18	6.10	0.74	7.4
194	♂	..	45	Polyarthritis with mitral lesion	.....	..	N	6	7.00	5.29	0.75	12.5
184	♂	W	30	Gonorrhea; arthritis	.....	..	.....	9½	7.63	5.29	0.69	7.2
	Average										0.74	
					B							
154	♂	C	42	Lobar pneumonia lower right with mitral regurgitation and arteriosclerosis	.....	..	103	13	6.90	6.30	0.90	7.0
155	♂	W	36	Lobar pneumonia	.....	..	100	12	8.28	6.70	0.80	6.6
156	♂	W	31	Lobar pneumonia	130/77	..	101.5	3½	7.40	6.20	0.83	23.7
107	♂	W	54	Lobar pneumonia	136/78	58	104	9	6.90	5.50	0.79	8.7
				Four days later	136/78	37	N	13	6.90	5.29	0.75	5.7
153	♂	W	36	Lobar pneumonia with streptococcus infection of shoulder	130/78	..	100.6	8	7.20	5.40	0.75	9.3
										Average	0.81	
158	♂	W	24	Lobar pneumonia (just after crisis)	.....	..	97.2	12	7.80	6.65	0.85	7.0
199	♂	W	35	Convalescent pneumonia	.....	..	N	8	7.41	5.50	0.74	9.2
157	♂	W	42	Convalescent pneumonia	120/40	..	N	13	6.33	4.69	0.74	5.7
170	♂	C	34	Convalescent pneumonia	.....	..	99	7	8.28	5.50	0.66	9.4
	Average										0.71	
					C							
233	♀	C	19	After bronchitis immediately postfebrile (6 months pregnancy and mitral insufficiency)	102/60	..	.....	6	6.66	5.49	0.82	13.6
214	♂	C	24	Immediately following defervescence; bronchitis	112/74	..	.....	15	8.28	6.70	0.81	5.4
110	♂	W	24	Postfebrile; had chill and temperature of 102	.....	..	.....	7¼	7.55	6.10	0.80	11.0
	Average										0.81	
					D							
5	♂	W	20	Normal, before influenza	.....	..	N	5	7.20	5.35	0.74	15.0
				During influenza	.....	..	104	5½	6.84	5.60	0.82	15.0
238	♂	W	30	Severe cold	108/54	..	N	6½	8.50	6.70	0.79	12.1
217	♂	W	23	Cold; sinusitis	.....	43	100	7	7.41	5.69	0.76	11.0
197	♂	W	25	Convalescent typhoid	120/40	..	N	6	8.40	5.80	0.70	11.6

ways during the last ten years and the significance in our concept of cardiorenal disease sufficiently emphasized so that the low degree of permeability here shown need not surprise us. That such low permeability in itself need not necessarily have a direct bearing on the

disease is obvious from the fact that many of our normal controls have an equally low rate.

We have examined only one child with nephritis (case 264, recurrent glomerulonephritis, extracapillary type) in which the capillaries were quite permeable, but the blister time retarded.

ACUTE INFECTIONS

In the group of acute infections (table 3) a number of deviations from the normal become apparent.

If we examine first a group of relatively mild infections (arthritis), the average age is 35, the blister time eight and one-half hours, the permeability ratio 0.74.

Five cases of lobar pneumonia during the course of the disease (average age, 38) had a blister time of nine hours (of these four had prolonged blister time and one a very short period). The permeability ratio was 0.81.

Immediately after the crisis (one case) the ratio was still 0.85 and the blister time still long (twelve hours).

During convalescence (four cases; average age, 41) the blister time was ten hours; the permeability ratio average 0.72.

It is obvious that during lobar pneumonia the capillaries are more permeable than usual, that the increased permeability persists immediately after the crisis and then returns to normal. On the other hand, the vessels have a predominatingly sympathetic tonus, with a resulting prolongation of the blister time which seems to persist even after the crisis.

In three postfebrile cases examined on the morning of, or the day following, defervescence (bronchitis and one undetermined infection, cases 110, 204 and 233) the permeability was high, 0.81.

In a student whose normal ratio was 0.74 the ratio was increased to 0.82 during influenza (temperature of 104 F.).

TUBERCULOSIS

Exudative tuberculosis and advancing tuberculosis in general (table 4) is associated with an increased permeability (ratio from 0.75 to 0.85). Some of these cases have a prolongation of blister time (skin sympathetically oriented), but the majority are normal in this respect.

Chronic tuberculosis is associated with a normal permeability of the capillaries and a normal blister time.

Exudative cases on treatment, with absorption of fluid and lowering of febrile curve, have a lessened permeability.

The relation of the type of tuberculosis to the relative autonomic tonus has been the subject of a number of recent papers, Guth,[9] in partic-

9. Guth, E.: Beitr. z. Klin. d. Tuberk. **60**:39, 1925.

TABLE 4.—*Tuberculosis*

Case	Sex	Race	Age	Clinical or Postmortem Diagnosis	Albumin	Casts	Blood	Non-protein Nitrogen	Phenolsulphonphthalein, per Cent	Mosenthal	Blood Pressure	Hemoglobin	Red Blood Cells	Temperature	Blister Time in Hours	Serum Protein, per Cent	Blister Protein, per Cent	Ratio B/S	R/T
249	♂	C	10	(1) Tuberculous peritonitis, six months duration	.....	..	..	..	..	..	.....	...	3,500,000	To 103	8	7.98	7.00	0.87	11.0
				(2) Tuberculous peritonitis (on treatment, temperature 99-100, fluid absorbing)	.....	..	..	..	..	..	.....	45	.....	....	12	8.92	4.72	0.53	4.4
250	♂	C	6	Tuberculous peritonitis (mild)..	.....	..	..	..	..	..	.....	80	5,000,000	To 100	5	8.28	6.80	0.82	16.4
225	♂	W	14	Tuberculous adenitis (pathologic report: little tendency toward fibrous induration)	.....	..	..	..	..	..	.....	100	.....	....	5¾	8.70	7.11	0.81	14.0
222	♀	W	6½	Early tuberculosis of hip (roentgen-ray examination negative)	.....	..	..	..	..	..	.....	...	.....	100 occasionally	4½	8.06	6.50	0.80	18.8
66	♂	W	14	Potts, psoas abscess; tuberculosis of axillary glands	.....	..	..	..	..	..	104/74	...	.....	101	6	7.85	6.10	0.78	13.0
				Repeated 2 months later.....	.....	..	..	..	..	..	.....	...	.....	102	5½	7.20	5.50	0.76	13.8
205	♂	W	8	Tuberculous arthritis (?) (roentgen-ray examination: pulmonary tuberculosis probable)	.....	..	..	..	..	..	.....	...	5,000,000	To 100	5	8.28	6.80	0.82	16.4
121	♂	W	37	Pleurisy and effusion.....	++	++	..	43	92	..	128/85	...	.....	....	7	7.20	6.15	0.85	12.1
35	♂	C	20	Tuberculous peritonitis and pleural effusion	.....	..	..	..	..	..	.....	...	6,000,000	....	6½	7.97	6.48	0.82	12.6
				(2) One week later on treatment	.....	..	..	..	..	..	.....	...	.....	....	5½	7.63	5.49	0.73	13.2
				(3) Five weeks later exudate all absorbed	+	++	..	38	..	..	.....	60	.....	....	6	8.92	6.70	0.75	12.5
	♂	W	15	Tuberculosis of right upper lobe, active (with nephritis)	.....	..	..	46	60	+	130/70	75	4,150,000	N	9½	7.12	5.80	0.81	8.5

73	♂	W	40	Renal tuberculosis; orchidectomy (pathologic report: advanced caseation testis)	+++	..	..	..	..	..	120/72	...	.....	....	6½	7.63	6.11	0.80	12.3
96	♂	W	30	Advanced peribronchial pulmonary tuberculosis with arthritis deformans	.....	..	..	40	70	..	112/74	60	4,000,000	....	5½	7.41	5.94	0.80	14.5
74	♂	W	35	Renal and genital tuberculosis; left testis removed years before; right testis one week before (pathologic report: chronic fibrosis of tuberculous testis)	+	..	++	43 R. K. = 5 L. K. = 15	..	.. 30 m.	.....	85	4,600,000	....	7½	6.98	5.60	0.80	10.6
51	♂	W	26	Right upper pulmonary tuberculosis, active (later became quiescent)	.....	..	..	..	..	..	.....	75	4,350,000	....	9½	9.25	7.11	0.77	8.1
252	♂	W	43	Old right upper, active.....	.....	..	..	36	..	..	.....	...	.....	....	7	7.85	6.10	0.77	11.0
201	♂	C	60	Pulmonary tuberculosis (Cook County Hospital); syphilis	.....	..	..	..	..	..	.....	...	.....	....	6	6.90	5.22	0.75	12.5
111	♂	W	23	Pulmonary tuberculosis (cavitation); tuberculous shoulder	.....	..	..	..	..	..	88/60	...	.....	N	7½	9.03	6.82	0.75	10.0
262	♂	W	43	Tuberculosis (?); dry pleurisy	.....	..	..	43	42½	+	120/60	...	.....	N	10	7.10	5.29	0.74	7.4
41	..	W	31	Pulmonary tuberculosis (cavitation)	.....	..	..	..	..	..	110/65	..	.....	....	6½	7.95	6.01	0.73	11.2
52	♀	W	20	Pulmonary tuberculosis (chronic)	.....	..	..	..	..	..	.....	...	.....	....	10	9.70	7.01	0.72	7.2
109	♂	W	36	Pulmonary tuberculosis (bronchiectasis)	+	Occasional	..	43	..	..	134/85	...	.....	....	5	8.70	6.32	0.72	14.5
216	♀	W	30	Pulmonary tuberculosis (chronic)	.....	..	..	43	..	..	120/78	80	4,250,000	....	5	7.85	5.60	0.71	14.2
64	♂	W	29	Tuberculosis of glands, bone, testis	.....	..	..	53	..	..	112/84	...	.....	....	6½	8.06	5.70	0.70	10.7
212	♂	W	40	Tuberculosis of kidney (right)..	Trace	..	..	34	..	..	106/78	...	.....	....	6	7.63	5.29	0.69	11.5
30	♂	W	51	Chronic fibrosis, tuberculosis and asthma (on epinephrine)	+	+	..	31	85	..	150/80	...	.....	....	6	7.63	4.89	0.64	10.6
98	♂	W	24	Tuberculosis of kidney 10 years before:															
				(1) Cystoscopic — one-tenth functional	.....	..	..	..	..	..	.....	...	.....	....	5½	8.38	5.23	0.62	11.2
				(2) Three weeks later.....	.....	..	..	40	..	..	132/98	...	.....	....	5¾	8.28	5.61	0.67	11.6

TABLE 5.—*Gastric and Duodenal Ulcer*

Case	Sex	Race	Age	Clinical or Postmortem Diagnosis	Albumin	Casts	Blood	Non-protein Nitrogen	Phenol-sulphon-phthalein, per Cent	Mosenthal	Blood Pressure	Hemoglobin	Red Blood Cells	Temperature	Wassermann Reaction	Blister Time in Hours	Serum Protein, per Cent	Blister Protein, per Cent	Ratio B/S	R/T
68	♂	W	45	(1) Duodenal ulcer (roentgen-ray examination) and low grade alcoholic amblyopia	—	Occasional	—	45	74	..	140/80	..	.....	Normal	A. C.	6	8.28	6.30	0.76	12.6
				(2) Repeated	..	..	..	..	..	..	.....	..	.....	.....	.....	6½	8.06	6.10	0.75	11.5
206	♂	W	34	Gastric ulcer	..	..	..	..	..	..	90/65	..	.....	Normal	—	6	6.98	5.49	0.78	13.0
115	♂	W	52	Gastric ulcer (lesser curvature)	—	Occasional	—	49	95	..	118/80	65	5,500,000	To 99	—	11	7.41	5.29	0.71	6.4
256	♀	W	47	Duodenal ulcer	—	—	—	77	75	..	120/78	90	4,000,000	Normal	—	6½	6.98	4.68	0.67	10.3
246	♂	W	40	Duodenal ulcer	..	..	..	..	..	..	.....	..	.....	.....	—	5½	7.85	6.10	0.77	14.0
		Average.....																	0.74	
10	♂	W	..	(1) Ruptured duodenal ulcer	..	..	..	..	..	..	.....	..	.....	.....	.....	6	8.28	6.10	0.73	12.1
				(2) Repeated 3 weeks later	..	..	..	..	..	..	.....	..	.....	.....	.....	6	8.00	5.29	0.66	11.0
				Necropsy: ruptured ulcer; healed tuberculosis of apex; cloudy swelling of kidneys; dilatation of left ureters and pelvis																
127	♂	W	69	Perforating ulcer of the stomach	—	Occasional	..	80	65	+	115/75	40	1,450,000	.....	.....	12	5.03	3.76	0.74	6.1
				Necropsy: ulcer of the stomach; kidneys: small interstitial scars and atrophic tubuli with hyaline obliteration of glomeruli; bronchial pneumonia; fatty myocarditis; atheromatosis of aorta																

TABLE 6.—*Carcinoma*

Case	Sex	Race	Age	Clinical or Postmortem Diagnosis	Albumin	Casts	Blood Pressure	Non-protein Nitrogen	Phenolsulphonphthalein, per Cent	Temperature	Red Blood Cells	Hemoglobin	Blister Time in Hours	Serum Protein, per Cent	Blister Protein, per Cent	Ratio B/S	R/T
									A								
94	♀	W	47	Carcinoma of breast.....	+	—	.....	..	..	Normal	.....	..	9	7.40	4.37	0.59	6.5
93	♀	W	49	Myxoma of abdominal wall	Trace	—	178/110	36	..	Normal	.....	..	18	8.18	4.89	0.60	3.3
28	♂	W	66	Carcinoma of gallbladder; arterioclerosis and arteriolosclerotic kidney	—	—	104/72	36	..	.....	.....	..	9	5.68	3.67	0.64	7.1
253	♂	W	69	Epithelioma on face.....	—	—	120/68	63	..	Normal	.....	..	7	8.06	5.40	0.66	9.4
131	♂	W	55	Carcinoma of esophagus with gangrene of lung; spondylitis deformans; A. S. larger vessels of kidney	—	+	110/75	39	..	.....	.....	..	9	7.20	5.09	0.69	7.6
29	♂	W	34	Thymoma—with both kidneys infiltrated with metastatic tumor nodules	..	..	.....	..	..	.....	.....	..	8½	7.08	4.89	0.69	8.1
187	♂	W	60	Carcinoma of esophagus...	..	..	.....	..	..	.....	.....	..	9½	8.28	6.10	0.73	7.7
204	♂	W	47	Carcinoma of larynx—tracheotomy; bronchial pneumonia (kidneys normal on necropsy	..	..	.....	..	..	.....	3,500,000	65	7½	6.98	5.82	0.83	11.0
				Average.....												0.67	
									B								
254	♂	W	54	Carcinoma of stomach.....	..	..	.....	50	75	Normal	4,400,000	65	12	7.63	5.23	0.68	5.6
183	♂	W	50	Carcinoma of stomach ?....	..	..	.....	..	..	.....	.....	..	9½	6.49	4.47	0.69	7.2
60	♂	W	38	Carcinoma of pylorus.....	—	—	.....	27	..	.....	1,170,000	25	5	8.18	5.90	0.72	14.4
59	♂	W	53	Carcinoma of stomach.....	—	—	110/70	43	..	.....	.....	..	7	8.48	6.10	0.72	10.3
													9	8.06	6.30	0.77	8.5
255	♂	W	68	Carcinoma of stomach.....	..	..	138/82	..	80	Normal	3,890,000	58	14	5.74	4.16	0.72	5.1
119	♀	W	48	Carcinoma of uterus; stricture of ureters; ascending pyelonephritis; beginning arteriosclerosis, hypostatic pneumonia	++	++	160/70	152	..	.....	.....	..	9	8.50	6.40	0.75	8.3
78	♂	W	53	Adenocarcinoma of stomach; metastases to liver, lymph glands, etc.; kidney normal	..	..	108/72	..	..	.....	2,000,000	20	6	5.90	4.47	0.75	12.5
				Average.....												0.72	

TABLE 7.—*Goiter*

Case	Sex	Race	Age	Clinical or Postmortem Diagnosis	Albumin	Casts	Blood Pressure	Basal Metabolic Rate	Hemoglobin	Red Blood Cells	Non-protein Nitrogen	Phenolsulphonphthalein, per Cent	Blister Time in Hours	Serum Protein, per Cent	Blister Protein, per Cent	Ratio B/S	R/T
248	♀	W	29	(1) Toxic adenoma	..	..	.....	....	..	.....	..	....	3	7.20	6.10	0.84	28.0
				(2) Five days after operation.	Trace	..	150/90	+88	..	.....	..	....	4½	7.02	5.98	0.85	19.0
140	♂	W	37	Exophthalmic goiter	Trace	..	108/64	+64	..	.....	..	....	5	6.66	5.70	0.85	17.0
223	♀	C	40	1) Exophthalmic goiter	..	..	142/88	+65	..	.....	..	....	5¼	7.00	6.00	0.85	16.0
				(2) Exophthalmic goiter	..	..	.....	+65	..	.....	..	....	4½	7.41	6.10	0.82	18.2
				(3) Exophthalmic goiter after operation	..	..	.....	....	..	.....	..	....	6	7.20	5.69	0.79	13.1
7	♀	W	43	(1) Exophthalmic goiter with some pulmonary tuberculosis (roentgen-ray examination)	Trace	..	128/70	....	..	.....	..	....	2½	6.33	5.09	0.80	32.0
				(2) Exophthalmic goiter	..	..	.....	+51	..	.....	..	....	3	6.12	5.09	0.83	28.0
				(3) Exophthalmic goiter after operation	..	..	.....	....	..	.....	..	....	2½	7.55	5.90	0.78	31.0
144	♂	W	25	Colloid goiter (had crisis after removal)	..	..	102/64	+18	..	.....	..	....	7½	7.85	6.16	0.78	10.4
15	..	..	..	Toxic adenoma	..	..	140/80	+62	..	.....	..	....	5	7.63	5.74	0.75	15.0
15b	♀	W	42	Exophthalmic goiter 3 years; crisis 1 month before; weight loss, 35 pounds	..	..	.....	+34	..	.....	..	....	6	7.30	5.49	0.75	12.0
207	♀	W	58	Exophthalmic goiter and arteriosclerosis	..	..	220/60	+68	..	.....	..	....	6	7.52	5.59	0.74	12.0
31	♀	W	50	Toxic adenoma; myocarditis and arteriosclerosis	+	Occasional	174/96	+50-70	50	6,000,000	38	....	7½	7.20	5.29	0.73	10.0
14	♀	W	45	Riedl struma (no clinical symptoms of exophthalmic goiter except weight loss, 10 pounds)	..	..	.....	+42	..	.....	..	....	5	8.28	6.04	0.73	14.6
M0	♀	W	32	Exophthalmic goiter	—	—	125/60	+75-100	..	.....	..	....	5	7.73	5.48	0.70	14.0
20	♀	W	37	Obesity; hyperthyroidism; weight 194 pounds; pulse 80	..	+	.....	+40-50	70	4,000,000	43	....	4	8.70	6.10	0.70	17.5
A	♀	W	52	(1) Exophthalmic goiter during remission	..	..	.....	....	..	.....	..	....	4	7.32	4.98	0.68	17.0
				(2) Blister on during operation	..	..	160/104	+25	..	.....	..	....	4	8.49	3.24	0.38	9.5
15c	♂	W	24	Exophthalmic goiter 6 years..	—	—	125/70	+60	80	5,700,000	..	....	4	7.95	5.30	0.66	16.5
13	♀	W	25	Partial thyroidectomy, 1918; still nervous	—	Occasional	118/80	+11	..	.....	32	42½	4	8.92	5.90	0.65	16.2

TABLE 8.—*Miscellaneous Medical Cases*

Case	Sex	Race	Age	Clinical or Postmortem Diagnosis	Albumin	Casts	Non-protein Nitrogen	Phenol-sulphon-phthalein, per Cent	Blood Pressure	Hemoglobin	Red Blood Cells	Temperature	Blister Time in Hours	Serum Protein, per Cent	Blister Protein, per Cent	Ratio B/S	R/T
43	♂	C	25	Acute gastritis.....	..	..	55	..	.....	70	4,000,000	..	13	7.00	5.90	0.84	6.4
143	♂	W	6	Hirschspring's disease (megacolon)	..	..	..	..	.....	..	.....	..	4¾	6.77	5.70	0.84	17.0
220	♀	W	15	Impacted feces (megacolon ?)	+	..	..	..	98/70	80	4,700,000	99	5	8.38	6.60	0.78	15.6
5	♀	W	26	Chronic appendix..	—	—	49	..	130/70	..	.....	..	6	8.70	5.70	0.65	11.0
147	♀	W	42	Cholecystitis.....	—	—	..	..	144/76	..	.....	..	4	8.49	5.77	0.67	16.7
257	♀	W	51	Arthritis deformans	Trace	Few	46	80	118/78	78	4,250,000	100	8	8.92	7.20	0.80	10.0
203	♂	W	58	Arthritis deformans; hypertrophied prostate; lipoma of buttock	—	—	40	..	141/85	..	.....	..	6	7.60	5.90	0.77	13.0
102	♂	W	51	Hypertrophic arthritis	..	..	..	..	.....	..	.....	..	6¼	7.30	5.50	0.75	12.0
16	♂	W	26	Asthma (2 years duration)	—	—	36	..	127/80	..	.....	..	4	8.98	6.20	0.69	17.2
258	♀	W	29	Asthma (on epinephrine)	..	..	..	..	.....	..	.....	..	6	8.92	6.10	0.68	11.3
18	♂	W	25	Postanaphylactic shock (sore throat, nausea, vomiting, skin eruption, (streptococcus infection ?)	..	..	..	50	122/68	..	.....	..	8	7.30	5.50	0.75	9.2

TABLE 9.—*Miscellaneous Medical Cases*

Case	Sex	Race	Age	Clinical or Postmortem Diagnosis	Albumin	Casts	Non-protein Nitrogen	Blood Pressure	Phenolsulphonphthalein, per Cent	Hemoglobin	Red Blood Cells	Basal Metabolic Rate	Temperature	Blister Time in Hours	Serum Protein, per Cent	Blister Protein, per Cent	Ratio B/S	R/T
26	♀	W	18	Obesity.....	—	—	38	115/70	—	87	4,800,000	+ 1	.....	6	7.96	6.70	0.84	14.0
213	♀	C	36	Diabetes insipidus..	—	++	25	.....	90	75	.....	Normal	.....	4½	8.06	6.50	0.80	17.5
55	♀	W	40	Obesity.....	—	—	46	110/60	60	80	4,200,000	+ 6	.....	5	8.49	6.50	0.78	15.6
259	♀	W	37	Obesity; hypertension	—	—	34	160/120	52	87	4,650,000	+12	.....	6	7.28	5.49	0.75	12.5
42	♀	W	32	Obesity and diabetes insipidus	..	..	49	145/80	..	..	.....	....	.....	5	8.28	5.70	0.68	13.6
71	♂	W	65	Syphilitic cirrhosis with ascites; alcoholic neuritis, February 5	Trace	Occasional	..	120/80	..	..	.....	....	.....	8	5.35	3.55	0.66	8.2
				(2) March 6.....	..	..	..	.....	..	..	.....	....	.....	8	4.59	3.45	0.75	9.3
				(3) March 26.....	..	..	..	.....	..	..	.....	....	.....	6	5.17	3.86	0.74	12.3
56	♂	W	50	Syphilitic cirrhosis; chronic fibroid phthisis; edema of brain; kidney with little pathologic change except hyperemia; no ascites	..	Occasional	28	.....	..	..	.....	....	.....	6	6.77	4.75	0.70	11.6
176	♂	W	61	Pernicious anemia	—	Occasional	57	120/70	60	30-40	1,240,000	....	Normal	5½	7.60	5.60	0.80	14.5
219	♀	W	38	Pernicious anemia; obesity	—	Occasional	36	180/90	50	..	1,640,000	+20	To 100	5½	7.41	5.60	0.75	13.6
265	♀	W	63	Paget's disease of bone	—	—	40	142/90		(Calcium 13.0)		....	Normal	7	7.20	6.40	0.88	12.5
				Paget's disease of bone, May 7	..	..	..	.....		(Calcium 8.5)		....	Normal	8	6.49	4.61	0.71	8.8
32	♂	W	21	Hodgkin's disease..	Trace	Occasional	34	104/65	45	80	5,000,000	....	Normal	6	8.28	6.50	0.78	13.0

ular, having studied the subject. We have shown in the group of normal persons that the group of low permeability contains many young men who have had more than the normal amount of pulmonary involvement, as determined by roentgen-ray examination and family history.

We believe it quite probable that the type of tuberculous reaction is determined by the relative tonus of the autonomic apparatus, of which the capillary permeability is in part an index. The permeability is of importance, moreover, because on its degree will directly depend, in a large measure, the type of reaction of the individual, i. e., whether exudative or proliferative.

In an article to be published elsewhere with Levinson we shall present a larger series of tuberculous cases and discuss the autonomic status in greater detail.

ULCER AND CARCINOMA

In five uncomplicated cases of ulcer of the stomach or duodenum (table 5) the permeability, as compared to the normals, is relatively high (average age, 43 years; average blister time, eight hours; permeability ratio, 74). It has frequently been suggested that in ulcer we deal with an autonomic alteration with a resulting spasm of the arterioles of the viscera. An increase in permeability such as we have here noted might be of interest in this connection.

The comparable cases of malignancy, seven in number (table 6), have a permeability ratio approximately the same, but the blister time is prolonged, so that the inflammatory index ratio is lower (carcinoma, 9; ulcer, 11).

The other cases of malignancy, with one exception, have a relatively low permeability and a prolonged blister time. Whether the difference is to be attributed to the age of the patients or to an increased sympathetic tonus of the skin we cannot at present determine. The lowering of the inflammatory index ratio would be in line with the general diminution of skin reactivity clinically observed in malignancy.

GOITER

Gänsslen observed that some of his cases of hyperthyroidism had short blister time, while cases of hypothyroidism formed a blister only after long periods.[5]

In the small series here reported (table 7) it will be observed that the blister time is relatively short (parasympathetic orientation of the skin) but that the permeability of the capillaries varies from 0.66 to 0.85. This variation has no relation to the degree of activity of the symptoms either clinically or as determined by the basal metabolic rate.

Much has been written concerning the rôle of the autonomic nervous system in its relation to hyperthyroidism. Efforts have been made to fit the peculiar symptoms into a distinct picture of hypersympathetic

tonus, despite the fact that many of the phenomena are distinctly parasympathetic in type. It is obvious that the skin must be parasympathetically oriented; otherwise, with the greatly increased metabolic rate, the patient would have a high fever. We have previously shown that the skin-visceral orientation is usually opposite in character.[6] This being the case, we can understand that hyperthyroidism is associated with a low sugar tolerance. We have a similar condition in generalized dermatitis, where, with an increased parasympathetic tonus of the skin, the clinical picture usually shows a lowered sugar tolerance, occasionally with glycosuria. This is occasionally noted in other skin disease and may be sufficiently impressive that the patient is treated for diabetes, despite the fact that such cases have nothing wrong with the pancreatic secretion.

Among the exophthalmic cases, those with low permeability frequently, but not always, have a high blood pressure or other evidence of vasomotor change.

It is of interest to note that the lowest permeability noted in our whole series of clinical cases was in patient A, in whom a blister formed during the period of operation contained only 0.38 per cent of the protein present in the blood serum.

Usually the permeability and sometimes the rate of blister formation is reduced after thyroidectomy, but the patients have been kept for only a short period after operation, so that our observations have been necessarily limited.

MISCELLANEOUS MEDICAL CASES

Among the miscellaneous medical cases (tables 8 and 9) the cases of obesity (five in number) have a relatively high permeability and a short blister time, so that we can definitely put them into the group of cases with parasympathetic skins. In view of the fact that obesity is not infrequently observed as a postencephalitic sequel (as is also polyuria), this change is of interest for we find a similar condition in the postencephalitic parkinsonian syndrome.

The cirrhosis is of interest in that there is evident an increase in permeability as the case progresses.

A very high ratio was found in a case of Paget's disease of the bones. This was in an obese woman of 63, with typical roentgen-ray and histologic findings. The ratio was 0.88, with a blood calcium of 13 and a low sugar tolerance. Epinephrine injection was followed by a lowering of blood pressure. During her stay in the hospital the condition improved and the permeability ratio became lower (0.71) while the blood calcium also became much lower (8.6 mg.). It may be recalled that Paget's disease of the bones has been frequently found associated with adenomas of the parathyroids.

TABLE 10.—*Nervous Diseases*

Case	Sex	Race	Age	Clinical Diagnosis	Albumin	Blood Pressure	Non-protein Nitrogen	Phenol-sulphon-phthalein, per Cent	Temperature	Wassermann Reaction	Basal Metabolic Rate	Blister Time in Hours	Serum Protein, per Cent	Blister Protein, per Cent	Ratio B/S	R/T
226	♂	W	46	(1) Postinfluenzal parkinsonian disease	..	.....	(Calcium 12)	..	.....	.....	....	6	7.20	6.30	0.87	14.5
				(2) After malaria infection	..	.....	..	..	.....	.....	....	5	6.45	5.20	0.80	16.0
21	♂	W	45	Postinfluenzal parkinsonian disease	..	.....	..	..	.....	.....	....	10	8.28	6.30	0.76	7.6
77	♀	W	36	Postinfluenzal parkinsonian disease	..	.....	..	..	.....	.....	....	4½	7.41	5.09	0.68	15.2
243	♀	W	32	Postinfluenzal corpora striata lesion	..	110/80	36	73	.....	.....	+24	4	7.34	5.69	0.77	19.0
169	♂	W	63	Delirium tremens.....	..	.....	..	..	100	.....	....	4½	7.63	6.00	0.78	17.3
118	♂	W	16	Paresis.....	..	.....	..	..	.....	+++	....	8½	7.50	6.30	0.84	10.0
72	♂	W	56	Paresis ?.....	..	.....	..	..	.....	Spl.	....	9½	7.30	5.50	0.75	7.9
57	♂	W	28	Corpora striata; syphilis ?	..	.....	..	..	.....	Spl.	....	7	8.28	6.10	0.74	10.5
135	♂	W	41	Tabes.....	..	.....	31	..	.....	+++	....	5	7.85	5.70	0.72	14.4
11	♀	W	19	Epilepsy since 12 years of age	..	.....	..	..	.....	.....	....	6	8.18	5.90	0.72	12.0
92	♀	W	34	Epilepsy since 18 years of age; burn of arm 10 days before	..	.....	..	..	.....	.....	+20	9	8.06	5.29	0.65	7.0
36	♀	W	19	Epilepsy since 10 years of age; burn of hand 2 weeks ago	++	.....	46	..	.....	.....	.....	6	8.70	4.68	0.54	9.0
139	♂	W	16	Little's disease with mental defect	..	.....	..	..	Normal	.....	....	5	8.01	6.60	0.82	16.4
235	♂	W	16	(1) Juvenile paresis.....	..	.....	..	..	.....	.....	....	10	7.74	6.20	0.80	8.0
				(2) After malaria (10 days later)	Trace	.....	..	..	.....	.....	....	6½	6.43	5.09	0.79	12.1
97	♂	W	11	Acromegaly, idiocy.....	..	.....	..	..	Spl.?	.....	....	5½	8.39	6.46	0.77	14.0
58	♂♀	C	6	Juvenile paresis.....	..	.....	..	..	.....	.....	....	7	8.00	6.10	0.76	11.0
12	♂	W	9	Traumatic epilepsy.....	..	.....	36	..	.....	.....	....	5	7.20	5.30	0.73	14.6

An acute gastritis patient had a high permeability with a sympathetic skin tonus (internal organs parasympathetic).

The cases of arthritis deformans were all relatively permeable. Clinically, we realize that arthritis deformans represents something much more profound than merely an expression of joint and bone change. Observations of such capillary changes would confirm the notion that we deal with a far reaching alteration of the metabolism.

NERVOUS DISEASES

In the group of nervous diseases (table 10), of which we have a few at the present time, the postencephalitic parkinsonian syndromes are of most interest. That a great variety of autonomic disturbances become manifest during encephalitis and postencephalitis is obvious, and indeed the skin changes may be of such a degree that actual blister formation may take place. The two most marked cases (cases 226 and 21) had a high permeability, both associated with a relatively high blood calcium. In a third case in which the acute phase had been passed some years before, the permeability was much lower (case 77).

In a single case of delirium tremens the patient had a high permeability and short blister time. Of two adult paretic patients, one had a high permeability, the other was at the upper margin of the normal (0.75). In both, the skin was sympathetically oriented.

During menstruation a distinct increase in permeability was observed in a case of epilepsy.

The readings were as follows:

January 14,	Ratio ± 0.72	R/T = 12.0
March 5	Ratio = 0.83	R/T = 18.3
March 9	Ratio = 0.79	R/T = 13.0
Menstruating		

Differences exist also in the capillaries of paralyzed extremities, as illustrated in a case of multiple sclerosis. The patient was aged 32; had paralysis of the right side for seven years and atrophy. The ratio in the left arm was 80, in the right arm, 90.

A second case, a small spinal cord cyst, showed no differences in permeability or blister time. This case had sensory but little motor change.

SURGICAL AND OPHTHALMOLOGIC CASES

Among the surgical cases examined, those with pathologic conditions in the kidney (table 11) have a low permeability, with the exception of one patient on hexamine. Many of the other patients examined shortly after some operative procedure had a high permeability, as will be seen from the table.

This increase in permeability is evident in ophthalmologic cases (table 12), usually associated with considerable pain. This may be

TABLE 11.—*Miscellaneous Surgical Cases*

Case	Sex	Race	Age	Clinical Diagnosis	Albumin	Casts	Blood	Non-protein Nitrogen	Blood Pressure	Temperature	Wassermann	Leukocytes	Blister Time in Hours	Serum Protein, per Cent	Blister Protein, per Cent	Ratio B/S	R/T
	♂	W	35	Kidney stone (blister on during operation)	+	..	+	..	132/90	.....	.....	.....	7	6.98	4.00	0.57	8.1
123	♂	C	27	Stenosis of ureters.....	+	..	+	38	125/80	.....	.....	.....	12	5.65	4.89	0.64	5.3
122	♂	C	77	Following prostatectomy 3 weeks previously (now on hexamine)	+	Occasional	..	50	128/84	.....	+++	.....	20	7.41	5.90	0.80	4.0
76	♂	W	48	Stricture of urethra.....	Trace	—	—	..	130/86	.....	.....	.....	5½	7.58	5.25	0.69	12.5
177	♂	W	7	Mastoid, chronic (not operated on)	—	..	..	..	.....	To 99	.....	.....	5	8.28	6.81	0.82	16.4
65	♂	W	33	Varicose veins; operated on 4 days previously	..	..	..	..	122/90	.....	.....	.....	7	6.98	5.70	0.81	11.5
234	♂	W	39	Ulcer of rectum (tuberculosis ?), cauterized 2 days previously, much pain	..	..	..	49	104/80	.....	.....	.....	6½	7.20	5.69	0.79	12.1
208	♀	W	38	Hemosalpinx and appendix; operated on 4 days previously	..	..	..	..	.....	.....	.....	.....	7	6.77	5.94	0.78	11.0
63	♂	W	48	Hernia; operated on 2 days before	..	..	..	..	134/90	.....	.....	.....	5½	7.63	6.00	0.78	14.1
80	♀	W	17½	Appendix removed 2 days previously (sclerosis of mucosa)	..	..	..	..	116/68	.....	.....	11,150	5½	8.33	6.50	0.78	14.1
99	♂	W	6	Osteomyelitis; calcis and femur opened 2 weeks previously	..	..	..	..	.....	To 100	.....	.....	5½	8.65	6.60	0.76	14.0
70	♀	W	32	Abscess of ilium (not operated on)	..	..	..	..	.....	To 100	.....	15,000	7	9.35	7.11	0.76	11.0
92	♂	W	30	Rectal abscess 4 days after patient was operated on	..	..	..	..	.....	.....	.....	.....	6	7.63	5.70	0.74	12.0
82	♀	W	43	Abdominal hernia 2 weeks after operation	..	..	..	..	.....	.....	.....	.....	5½	7.63	5.78	0.74	13.5
101	♂	W	31	Postcholectomy 6 days after operation	..	..	..	49	108/80	.....	.....	.....	5½	6.76	4.59	0.68	12.3

due to a more or less direct stimulation of the vagus as a reflex. In the table we have separated the juvenile cases from the adults because of their normal difference in permeability. It is nevertheless apparent that both groups have a relatively high rate, but that the rate of blister formation is not increased so that the inflammatory index ratio is rela-

TABLE 12.—*Ophthalmologic Cases*

Case	Sex	Race	Age	Clinical Diagnosis	Albumin	Blood Pressure	Non-protein Nitrogen	Blister Time in Hours	Serum Protein, per Cent	Blister Protein, per Cent	Ratio B/S	R/T
215	♂	W	8	24 hours after operation for strabismus	..	.....	..	4	7.20	6.40	0.88	22.0
241	♀	W	13	24 hours after operation for strabismus	..	.....	..	3½	8.39	7.11	0.84	24.0
116	♀	W	13	Left phlyctenular keratitis	..	.....	..	5½	7.85	6.60	0.84	15.0
130	♀	W	12	24 hours after operation for strabismus	..	.....	..	7	8.07	6.80	0.84	12.0
227	♀	W	8	24 hours after operation for strabismus	..	.....	..	6½	7.85	6.10	0.79	12.1
229	♂	W	12	24 hours after needling congenital cataract	..	.....	..	5½	8.49	6.50	0.76	13.8
130	♀	W	13	Congenital cataract	..	.....	..	6	8.10	5.37	0.64	10.6
	Average										0.80	
54	♀	W	64	Postoperative iridocyclitis (on acetylsalicylic acid, amido pyrine and atropine)	+	220/90	..	8	7.04	5.70	0.80	10.0
183	♂	W	59	Orbital cellulitis (tumor ?)	+	180/80	69	8	8.50	6.77	0.80	10.0
79	♂	W	29	Bilateral uveitis	..	.....	..	5	7.47	5.90	0.79	16.0
247	♂	W	65	24 hours following cataract extraction	..	.....	..	8	7.63	5.90	0.77	9.6
228	♂	W	77	Ulcerative keratitis	..	.....	..	7	8.28	6.50	0.77	11.0
174	♂	W	23	24 hours after needling for traumatic cataract	..	.....	..	7½	7.00	5.40	0.77	10.0
260	♀	W	66	24 hours after extraction of senile cataract	..	.....	..	9	8.71	5.49	0.63	7.0
24	♀	C	27	Iritis.....	..	.....	..	7	9.13	6.60	0.72	10.0
	Average										0.75	

tively low. Whether the relative susceptibility to surgical shock and to intoxication from the absorption of the lens protein bears some relation to the alteration in permeability seen in these cases we cannot state.

COMMENT

It is evident from these studies that distinct differences exist in the degree of capillary permeability observed by the blister method and that differences in the relative tonus of the arterioles can be determined when we study the blister time.

Generally, as we might anticipate, increase in capillary permeability goes hand in hand with a reduction in the blister time (parasympathetic tonus), the most striking example occurring in the case of generalized dermatitis. Other skin conditions apparently have a similar orientation, even if not to the same degree. It holds true for some cases of exophthalmic goiter.

Conversely, in lowered permeability we find the longest blister time, as for instance in some of the cases of arteriosclerosis and hypertension and epilepsy. Presumably these are distinctly sympathetic as far as the skin is concerned, although Kylin [10] has demonstrated that as far as the reaction to epinephrine is concerned cases of essential hypertension react with a vagotonic blood pressure curve.

But the capillary permeability and the apparent tonus of the arterioles need not be parallel. In the arteriosclerotic case with decompensation we may find high permeability (to 0.90) with a prolonged blister time, i. e., spasm of the musculature continuing with a damaged or fatigued capillary endothelium. We find a similar condition in an acute infection, such as lobar pneumonia; we find such cases not infrequently in tuberculosis.

On the other hand, we find the exophthalmic patient presenting uniformly a short blister time (parasympathetic orientation of the arterioles) with a variable permeability. Frequently the latter is high (0.85), occasionally reduced. (During operation in one case the ratio was the lowest observed in this entire series.)

When we review the various clinical conditions, the small group of skin diseases illustrates that the capillaries of the skin as a whole are changed in such conditions as dermatitis herpetiformis and eczema, as well as those conditions described by Gänsslen. This is quite in accord with the work of Müller,[11] who has studied the reaction of the capillaries by means of the peripheral leukocyte count, and the work of Pulay,[8] who has studied the biology of the skin reactions from the dermatologic point of view. Parasympathetic orientation of the skin is associated usually with sympathetic orientation of the viscera, i. e., lowered sugar tolerance.[12]

With cardiac decompensation the capillaries become quite permeable, and this is obviously to be regarded as one of the factors in the production of edema. But the orientation of the arterioles may be sympathetic, i. e., spastic, as, for instance, with decompensation of hypertension. In nephritis, likewise, the capillaries may be permeable but the arterioles

10. Kylin, E.: Klin. Wchnschr., no. 26, 1924, p. 28.

11. Müller, E. F.: Involuntary Nervous System: An Important Factor in Body's Resistance, Arch. Int. Med. **35**:796 (June) 1925.

12. Pulay, E.: Stoffwechsel und Haut, Berlin, Urban and Schwartzenberg, 1925.

spastic. Kidney conditions associated with strictures (urethra, ureters) have a low capillary permeability.

In general, we can state that some evidence of capillary injury (or fatigue) with increased permeability is apparent with albuminuria and occasional casts in the student group. These may show either a rapid or slow blister time and there is, as a rule, no striking change in the blood pressure. In an advanced case of recurrent glomerular nephritis (extracapillary type) the permeability was high, the blister time retarded (blood pressure high). Chronic nephritis associated with hypertension means spastic arterioles but in addition a capillary wall with retarded exchange.

Acute infection is associated with increased permeability and relatively sympathetic skin tonus, which, with the increase in metabolic rate, plays its part in the retention of heat and the phenomenon of fever. The increase in permeability is seemingly a transient affair for it is apparent for only some twenty-four hours after defervescence. Meyer [13] has called attention to the general phenomenon of parasympathetic overtonus during defervescence.

Chronic tuberculosis is associated with normal or diminished permeability and sympathetic orientation of skin arterioles. This plays a part in the relative lability of the temperature reaction of the tuberculous person. Presumably such an orientation (generally sympathetic) is of benefit to the tuberculous person because of the diminution of absorption that it entails. The advancing type of tuberculosis is associated with relatively high capillary permeability, although the skin arterioles may remain sympathetically oriented.

Ulcer of the stomach and duodenum was found associated with an increase in permeability. I do not wish to enter into a discussion of the rôle of the autonomic unbalance which has been described in connection with these conditions. The results would lend some support to such a concept as a factor in the etiology.

The same holds true for exophthalmic goiter. It is clinically known that the autonomic symptomatology and particularly the vasomotor phases of the disease may be quite dissociated from the activity of the process as measured by the metabolic rate or the general condition of the patient. Indeed, many of the vasomotor phenomena may remain apparent long after the basal metabolic rate has returned to normal following thyroidectomy. Our cases give evidence of similar character. Throughout all the cases the blister time is diminished, as has previously been found by Gänsslen. The skin arterioles are distinctly parasympathetic in orientation, accounting in a general way for the afebrile course of the

13. Meyer, H. H., and Meyer-Gottlieb: Experimentelle Pharmakologie, ed. 6, Berlin, Urban and Schwartzenberg.

disease despite its high metabolic rate. The permeability, however, is subject to great variation. Some cases are very permeable; others with equal activity have a normal or retarded rate. In general, the latter cases are those with higher blood pressure, but there are exceptions.

That the capillary permeability depends on the ionic equilibrium of the tissues is best illustrated in the case of Paget's disease, in which with high blood calcium (low tissue calcium) the permeability is increased and with low blood calcium (higher tissue calcium) the permeability is retarded. These studies will be taken up in detail in a later article. Similar conditions prevail in the nervous diseases studied. Particularly in the epileptic cases we find that the increased frequency of attacks in the young women studied was associated with increased permeability in the premenstrual and menstrual days.

Patients following surgical operations as well as ophthalmologic patients with considerable pain present an increase in permeability. We assume that this is in part to be ascribed to the anesthetic, in part to the resorption of tissue protein, and in part to a reflex of effect (perhaps as an indirect metabolic effect in the sense of Hamburger's "humoral transmission of nerve impulses") from the sensory stimulation.

SUMMARY

Capillary permeability of the skin vessels and the relative autonomic tonus of the arterioles has been studied by means of the cantharides blister.

Maximum permeability and parasympathetic tonus are found in generalized dermatitis.

Decompensation is associated with increased permeability. When due to renal or arteriosclerotic changes, the skin tonus may remain sympathetic.

Glomerulonephritis is associated with increased permeability with sympathetic arteriole tonus.

Chronic nephritis (arteriosclerotic) is associated with diminished capillary permeability and sympathetic arteriole tonus.

Acute infections show increased permeability with normal or increased sympathetic tonus. The increase in permeability persists immediately after defervescence.

Chronic tuberculosis shows normal or diminished permeability with normal or increased sympathetic tonus; advancing tuberculosis, an increase in permeability. Improvement is coincident with a diminution of capillary permeability.

Ulcer of the stomach and intestine shows a relatively high permeability; carcinoma, a somewhat lower range. This may be due to differences in the age groups.

Exophthalmic goiter has a distinct parasympathetic arteriole tonus but the permeability may vary from high to low. The cases with low permeability are usually those with a high blood pressure. The degree of permeability bears no relation to the basal metabolic rate.

Paget's disease of the bones and arthritis deformans have an increase in permeability. The same holds true for postencephalitic parkinsonian syndromes and for obesity.

Following surgical operations the permeability is increased and a similar condition is found in ophthalmologic cases with or without operation. This may be due to the anesthesia, to the resorption of necrotic material, or to reflex effects from the pain associated with these conditions.

TOLERANCE IN RESPECT TO THE MENINGOCEREBRAL MANIFESTATIONS OF ACUTE AND SUBACUTE LEAD POISONING

EXPERIMENTAL PRODUCTION *

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Clinical studies of human lead poisoning, particularly those of a statistical nature, have from time to time resulted in the conclusion that some degree of tolerance to the manifestations of this condition may be acquired through prolonged exposure to lead. The possibility of such an acquisition and the fact of its occurrence have been just as vigorously denied from other sources. It is the purpose of this article to show by an experimental method that, with the animal species used and methods employed, there can be demonstrated a marked degree of tolerance to the meningocerebral manifestations of lead poisoning. Thus, in still another instance has a clinical belief developed through careful case observation and statistical analysis found verification, although somewhat tardily, through laboratory investigation.

Tanquerel des Planches [1] in discussing a tabular survey of cases of lead encephalopathy said, "This table proves, among other things, that the greater number of patients have been exposed only a short time to lead preparations." And again, "The habit of frequent exposure to lead preparations does not prevent their action, but probably lessens their effects." The last clause indicates a belief in some degree of tolerance, but a contrary opinion is expressed somewhat later in the same discussion in these words: "But let them be once affected with encephalopathy, then, after their cure, they will be more liable to contract this disease than before being attacked with it, if they return at once to their labors."

Modern statistics, properly corrected for other variable factors, seem not to support the contention of Tanquerel des Planches that the greater number of patients have been exposed only a short time to lead preparations. Newman, McConnell, Spencer and Phillips [2] found that

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* Abstract presented at the meeting of the Association of American Physicians, 1926.

1. Tanquerel des Planches: Lead Diseases, translation by Dana, edition of 1850, p. 271.

2. Newman, B. J.; McConnell, W. J.; Spencer, O. M., and Phillips, F. W.: Lead Poisoning in the Pottery Trades, Public Health Bulletin no. 116, 1921, U. S. Public Health Service, Washington, D. C., p. 120.

in the pottery trades the rate of plumbism increases with the years of exposure. For males exposed less than one year the rate of positive plumbism was found to be 1.1 per cent; from one to five years, 5.6 per cent; from five to ten years, 6.5 per cent, and more than ten years, 13.4 per cent. The average length of exposure of the male positive group was found to be seventeen years.

No one has stated more emphatically a belief in an acquired tolerance in clinical lead poisoning than have Legge and Goadby.[3] Their definite statements on this point are worth quoting in full.

> The experience of all persons engaged in the routine examination of lead workers is that, although a worker may show signs of lead absorption as distinguished from definite lead poisoning during the earlier period of his employment, he later shows less and less signs of the influence of the poisonous substance; even a mild degree of definite poisoning in the early stages of work in a lead process does not seriously militate against this gradually acquired tolerance. . . .
>
> Such statistics as are available on this point show that an increased tolerance to the poisonous influence of lead is gradually acquired during periods of work, in that the number of attacks of poisoning diminish in frequency very considerably in relation to the number of years worked. . . . The greatest number of cases occur in persons who have only worked a short time in lead. . .
>
> In persons employed in lead trades some species of tolerance is generally developed, and if the functions of the body progress in the normal way the balance of intake and elimination are equal. . . .
>
> In many persons who have worked in lead for long periods, wasting does not progress beyond a certain point, and these persons may be regarded as having established a certain degree of immunity. . . . Such persons are either immune from the commencement, or they have established a certain degree of tolerance toward the metal; the latter supposition is the more probable, as there is reason to think that several of them suffered from mild degrees of poisoning during the earlier years of their employment.

In the recent monograph by Aub, Fairhall, Minot and Reznikoff[4] there is no reference to immunity in lead poisoning other than to those long recognized differences in susceptibility which are, in part, of an individual nature and, in part, are dependent on race, sex and age. The possibility of an acquired tolerance is not considered. This is in accord with the toxicology of lead as usually taught. Sollman[5] states that there is no acquired tolerance to lead, but that the natural susceptibility varies greatly as concerns the time, severity and symptoms of poisoning. These variations he attributes to differences in personal and factory hygiene, absorption and excretion, general health and resistance, and to other unknown factors.

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3. Legge, T. M., and Goadby, K. W.: Lead Poisoning and Lead Absorption, New York, Longmans, Green & Co., 1912, pp. 28, 29, 38 and 113.

4. Aub, H.; Fairhall, L. T.; Minot, A. S., and Reznikoff, P.: Lead Poisoning, Baltimore, Williams & Wilkins Company, 1926.

5. Sollman, T. H.: A Manual of Pharmacology and Its Application to Therapeutics and Toxicology, Philadelphia, W. B. Saunders Company, 1922, p. 938.

The importance of the establishment of the possibility of an acquired tolerance in lead poisoning reaches beyond this metal alone. It is improbable that a specific antitoxic substance such as is developed against bacterial toxins, snake venoms and vegetable toxalbumins of the type of abrin and ricin will be found to explain such an immunity, if it does exist. A protective mechanism based on lessened absorption, accelerated excretion, destruction by oxidation or reduction or the formation of less toxic compounds ought rather to be looked for. Perhaps living cells "learn" how to vary their metabolic processes in such a way that they are affected less deleteriously subsequently than in their first experience with the toxic substance. At any rate, if alterations in the structure or in the behavior of the animal body can be produced of such a nature as to render it relatively tolerant to certain manifestations of one heavy metal it is fair to assume that similar mechanisms can be called out for other poisons of the same general group. Clinical evidence of a fragmentary nature, indicating that this is true, ranges from the reputed arsenic tolerance of Styrian peasants to the recent observation of Young, Hill and Scott [6] that in the administration of mercurochrome-220 second and third injections equal in size to the first almost always produce less reaction and that not infrequently there is no reaction following a dose that produced a very severe reaction at first.

Experimental evidence for the production of tolerance to heavy metal poisoning, while not abundant, has appeared from time to time in the literature. Much of this is buried in protocols of experimental work bearing titles that give no clue to the fact that such important observations are included. Chittenden and Lambert,[7] however, as early as 1889 recognized the significance of the relative tolerance to uranium salts which they found to occur in a dog to which ascending doses were being administered. After a period during which no uranium was given, approximately ten times the original dose was necessary in order to produce the same evidences of intoxication. It is not clear that due allowance was made for lagging of the signs of poisoning behind the actual period of administration. West [8] was aware of this observation and, during experimental treatment of diabetes mellitus with uranium nitrate, found that with one of his patients it was necessary to give very much larger doses in order to get the same therapeutic effect as before,

6. Young, H. H.; Hill, J. H., and Scott, W. W.: The Treatment of Infections and Infectious Diseases with Mercurochrome-220 Soluble, Arch. Surg. **10**: 813-924 (May) 1925.

7. Chittenden, R. H., and Lambert, A.: Untersuchungen über die physiologische Wirkung der Uransalze, Ztschr. f. Biol. **25**:513-532, 1889.

8. West, S.: Uranium Nitrate in Diabetes Mellitus, Brit. M. J. **2**:467-472, 1895.

if uranium-free intervals had elapsed. Later, Suzuki [9] made the interesting observation, based however, on meager evidence, that regenerated renal epithelium following uranium poisoning showed remarkably less susceptibility to a subsequent exposure to the same or a larger dose. This regional acquired immunity was further investigated by Gil y Gil,[10] who found that rabbits poisoned with uranium nitrate would survive many times the lethal dose if graduated doses separated by proper intervals were administered in series. He thus produced in seven animals varying degrees of tolerance to uranium nitrate administered subcutaneously and intravenously. Similar results were obtained with mercuric chloride. He believed the acquired immunity to reside in the renal parenchyma itself and that it was developed unequally in different segments of the glomerulotubular system so that one portion might still be susceptible after another had become relatively resistant.

As to the experimental production of tolerance in lead poisoning, a rather complete search of the literature gives no indication that this has been accomplished hitherto. Legge and Goadby [11] found that in certain dusting experiments the animals maintained a state of equilibrium and even a certain degree of tolerance to the effect of lead dust, in that their weights remained almost constant. When the lead content of the air was as low as 0.00001 Gm. per liter, in more than one instance, after an initial diminution in weight, recovery of the lost weight took place. However, an increase in the quantity of lead dust present in the air immediately produced progressive loss in the body weight. There is no evidence that, under the conditions of the experiment, any important increase in resistance to lead was developed.

Reduced to its simplest terms the demonstration of experimentally produced tolerance to any poison consists of three steps. In the first place it is necessary to select some manifestation of the poison as an indicator of the degree of intoxication. Next, some quantitative expression of the dosage that normally produces this effect must be determined. Finally, it must be shown that under identical conditions of administration animals have gained the power of withstanding a considerably larger dosage without a corresponding appearance of the manifestation previously selected as an indicator.

The choice of the test manifestation is of the greatest importance. In experimental lead poisoning such indications of intoxication as loss of weight, palsy and the appearance of stippled cells in the blood lack the factor of definiteness which a good indicator of an "end reaction" should have. They are capable of appearing in such slight degrees that

9. Suzuki, T.: Zur Morphologie der Nierensekretion, Jena, 1912.

10. Gil y Gil, C.: Die Immunität im Nierenepithelgewebe, Beitr. z. path. Anat. **72**:620-653, 1923-1924.

11. Legge and Goadby (footnote 3), pp. 31 and 83.

the presence or absence of the test sign becomes problematical. The lethal effect of the intoxication may, of course, be used as the indication of relative susceptibility and possesses the quality of sharp definition in the highest degree. But death of the animal in the second step of the proof means that tolerance is never demonstrated in the same animal in which the normal intoxicating dosage has been determined. The comparison under such circumstances has to be between the apparent resistance of particular animals and the known susceptibility of a group of animals of similar species, age, sex and weight. The proof of acquired tolerance is more convincing when it rests, at least in part, on the performance of the same animals before and after the acquisition of the greater resistance to the poison. For this reason lethal effect is not the best criterion that can be selected. It is desirable, also, that the test manifestation should be one that does not show too long a latent period for its development. If it does, uncertainty may exist as to which stage in an ascending scale of dosage was sufficient to produce it. For the same reason, conditions that are to any considerable degree dependent on a cumulative action of the poison are not well suited to this purpose.

In the meningocerebral manifestations of experimental lead poisoning, particularly as exhibited by the guinea-pig, we have an indication of intoxication that is especially well adapted to the investigation of tolerance. If lead compounds be administered by mouth in suitable amounts practically all guinea-pigs within a short time develop characteristic convulsive seizures closely resembling those found in human lead meningoencephalopathy. After showing increased excitement and a behavior interpretable as a state of apprehension, the animal passes suddenly into a violent clonic convulsion, rushing madly around its cage and throwing itself headlong against the walls or any object in its way. This lasts for a few seconds only. Then the animal drops motionless in an equally severe tonic phase. There is usually a slight degree of opisthotonos but every skeletal muscle is involved and respiration is suspended. After an interval varying from a few seconds to a minute or more the tonic contraction begins to pass off and soon the animal takes short gasping respirations and gradually recovers, although remaining dazed or lethargic, rarely actively delirious, for some time. Death may occur during the first, or in a subsequent, convulsion and seems to depend primarily on suspension of respiration. If the animal is taken up at once during the tonic phase and artificial respiration applied its life may be saved when it would otherwise die. So violent is the clonic phase that it will always be noted by an attendant in or near the animal room, facilitating an accurate record of the occurrence of convulsions. Even when the seizures come at night, record is still possible since, in the usual type of wire cage, the animals practically always receive

abrasions on the nose from dashing against the walls. In male animals there is a discharge of semen during the convulsion. This coagulates quickly and remains for some time as a plug in the penile sheath. Inspection of such animals in the morning permits accurate tabulation of convulsions occurring during the night. Because of this special advantage male animals chiefly have been used for the experimental series here reported.

From this brief description of the characteristic epileptiform convulsion of lead meningo-encephalopathy in the guinea-pig it will be seen that this reaction lends itself very well for use as an indicator in statistical study. It either does or does not occur. Examined critically, it has only one disadvantage and that, fortunately, is not of serious importance when many animals are being used. This is the fact that when an animal is severely poisoned with lead a convulsion may be precipitated by excitement or by a sudden noise, such as the banging of the cover of the cage. If one of four animals in a cage has a convulsion one or two of the others may develop convulsions while the first is dashing about in its clonic phase. It might at first thought appear that this would introduce a double error, causing false positives in animals that would not spontaneously develop convulsions and leaving in the negative group equally, or even more severely, poisoned animals that happened to have escaped any inciting factor. It seems certain, however, that when convulsions are precipitated in this manner they occur only somewhat prematurely and that practically all such animals would exhibit convulsions later anyway. Since many animals having convulsions do not die, it is possible to test for tolerance in respect to this manifestation on animals known to have been previously susceptible to a certain amount of lead. In any investigation of tolerance, this constitutes an important advantage.

In the various series of animals utilized in this report, lead, in the form of commercial white lead or of chemically pure lead carbonate, was administered by mouth in gelatin capsules. The amount given was obtained by taking the average weight of the tared contents of all the capsules in a given batch. Greater accuracy was obtained by using a diluent and filling the capsules completely with the mixture. For this purpose linseed oil and cornstarch were used with commercial white lead, and cornstarch alone with lead carbonate. The animals were kept on a standard diet that has proved adequate for many years in a colony of guinea-pigs maintained as controls and for breeding purposes. The small range of dosage used in the reported series (from 0.126 to 0.171 Gm. of commercial white lead and 0.155 Gm. of chemically pure lead carbonate) was made possible through previous experience with this method of administration and was known to be an amount that would produce convulsions in untreated animals after about four

consecutive daily doses. No effort was made to determine the amount of lead absorbed. This could be found approximately by taking the difference between the amount administered and that recovered from all of the feces of each animal, collected separately and uncontaminated with urine. It was felt that the information thus obtained, while of the greatest importance in investigating the mechanism of tolerance, was not essential to a demonstration of the fact of the acquisition of tolerance. The reason for this will be considered in the discussion of the results. Of greater importance is the length of time during which fresh supplies of lead are made available for absorption, for dosage depends not only on the amount given but also on the rate and duration of administration. These factors as influencing the acquisition of tolerance must be the subject of a later article. In all series of animals used in this report one capsule was given each day during the period of lead intake.

TABLE 1.—*Determination of Lethal Dosage of Lead Carbonate*

Guinea-Pig	1	2	3	4	5	6	7	8	9	10	11	12	13	14
X149	250 Pb	Pb	Pb	..	..	..	..	..	..	..	..	..	†	..
X150	675 Pb	Pb	Pb +	..	.. +	..	..	..	..	†	..	..	..	..
X151	665 Pb	Pb	Pb	..	..	.. +	..	..	..	..	..	..	..	..
X152	585 Pb	Pb	Pb	.. +	.. +	..	..	.. +	..	..	..	..	..	..
X153	600 Pb	Pb	Pb	Pb	Pb	..	.. +	†	..	..	..	..	..	..
X154	685 Pb	Pb	Pb	Pb	Pb	..	.. +	†	..	..	..	..	..	..
X155	535 Pb	Pb	Pb	Pb	Pb	..	..	.. +	..	..	†	..	..	..
X156	675 Pb	Pb	Pb	Pb	Pb	..	..	.. +	†	..	..	..	..	..

In this and the following tables, Pb indicates a single administration of lead, in this case 0.155 Gm. of chemically pure carbonate of lead; the plus sign, the occurrence of convulsions; the dagger, death of the animal.

This table illustrates the method of determining the convulsion producing and lethal dosage of lead carbonate. Three doses of 0.155 Gm. each given on consecutive days produce convulsions and may kill. Five such doses not only produce convulsions but are always lethal.

The amount of lead carbonate, administered as described, capable of producing convulsions in animals with no previous exposure to lead is shown in the tabulated protocols given here. For instance, in table 1 is shown a test series for the determination of the convulsion producing and lethal dosage of lead carbonate. The column at the left designates individual guinea-pigs by number; the figures across the top, days of the experiment. The initial weight of each animal is given in grams for the first day. Pb indicates a single administration of lead, in this case

0.155 Gm. of chemically pure carbonate of lead; the +, the occurrence of convulsions; the †, death of the animal. Guinea-pig X149, dying on the thirteenth day, was never seen to have a convulsion, although its death makes it practically certain that its reaction was not exceptional in this respect. If we make this assumption, it will be seen that three consecutive daily doses of this size will produce convulsions and may kill while five such doses produce convulsions and cause death of all animals so treated. These results, with others not tabulated, may be summarized as in table 2; in each instance the number of doses given means the number of consecutive doses administered.

TABLE 2.—*Effect of Commercial White Lead and Chemically Pure Lead Carbonate (Mallinckrodt)*

Commercial White Lead	
4 doses of 0.126 Gm. produced convulsions in	12 of 12 animals
2 doses of 0.162 Gm. produced convulsions in	2 of 4 animals
1 dose of 0.171 Gm. produced convulsions in	1 of 4 animals
2 doses of 0.171 Gm. produced convulsions in	1 of 1 animals
3 doses of 0.171 Gm. produced convulsions in	3 of 3 animals
4 doses of 0.171 Gm. produced convulsions in	2 of 2 animals
Chemically Pure Lead Carbonate (Mallinckrodt)	
3 doses of 0.155 Gm. produced convulsions in	3 of 4 animals
4 doses of 0.155 Gm. produced convulsions in	2 of 2 animals
5 doses of 0.155 Gm. produced convulsions in	6 of 6 animals

It will be noted that within the range of size of dose used, four consecutive daily doses produced convulsions in every instance and three consecutive daily doses in every case but one. As to the lethal effect, all untreated animals receiving five consecutive daily doses of either form of lead and ten out of sixteen receiving four consecutive daily doses died. Under these conditions of administration, then, it may be stated in a general way that all animals receiving four or more consecutive doses develop convulsions and that those receiving five or more doses die. This establishes the quantitative relation subsequently made use of in determining whether or not there has been a gain in tolerance.

In the course of another group of experiments in which it was necessary to obtain material for histologic examination of the central nervous system of animals dying in convulsions after the oral administration of lead,[12] it was found that those guinea-pigs which survived convulsions required a longer period of lead administration in order to induce this manifestation a second time. This observation became the basis for the series of experiments reported here. It was soon found that the most important factor, apparently, leading to relative tolerance in respect to this evidence of lead poisoning was the interpolation of recovery periods between the periods of lead administration. In table 3

12. Weller, C. V., and Christensen, A. D.: The Cerebrospinal Fluid in Lead Poisoning, Arch. Neurol. & Psychiat. **14**:327-345 (Sept.) 1925.

TABLE 3.—*Induced Tolerance for Commercial White Lead*

Guinea-Pig	1	2	3	4	11	12	13	14	15	16	35	36	37	38	39	40	41	42	43	44	45	46	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83
X119	330 Pb	Pb	Pb	Pb	280 Pb	Pb	Pb	Pb	Pb	283 Pb	295 Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	298 Pb	300 Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	347 Pb
X120	460 Pb	Pb	Pb	Pb	Died on seventh day; weight, 389 Gm.																																			
X121	470 Pb	Pb	Pb	Pb	Died on eighth day; weight, 365 Gm																																			
X122	320 Pb	Pb	Pb	Pb	Died on seventh day; weight, 275 Gm.																																			
X123	370 Pb	Pb	Pb	Pb	Died on fifth day; weight, 320 Gm.																																			
X124	360 Pb	Pb	Pb	Pb	315 Pb	Pb	Pb	Pb	Pb	Died on sixteenth day; weight, 340 Gm.																														277 Pb
X125	370 Pb	Pb	Pb	Pb	330 Pb	Pb	Pb	Pb	Pb	327 Pb	362 Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	310 Pb	320 Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	288 Pb
X126	310 Pb	Pb	Pb	Pb	300 Pb	Pb	Pb	Pb	Pb	325 Pb	362 Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	337 Pb	345 Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb

Pb = 0.126 Gm. of commercial white lead (0.162 Gm. after seventy-eighth day).

Three out of eight animals were able to withstand sixteen consecutive doses of white lead, four times the convulsion producing dose and three times the lethal dose, without either convulsions or death resulting, although all three of these animals had shown convulsions following the first series of but four similar doses.

is shown a condensed protocol illustrative of the method used. This table is constructed on the same plan as was table 1 except that symbols indicating convulsions and death do not appear on it. All of the eight guinea-pigs in this group had convulsions following the first period of lead administration. The day of death and weight in grams at death of the five that died appear in their proper positions. The resting intervals between successive periods of lead administration are shown by the gaps in the series of consecutively numbered days of the experiment in the upper line of the table. It will be seen that four of the eight animals in this particular series died following the first period of lead administration, which consisted of four doses. A rest period of six days intervened and the survivors were then given six similar consecutive doses. One was lost during this period. After a rest period of eighteen days, the three survivors withstood twelve consecutive daily doses without convulsions, and finally after a rest period of twenty-one

TABLE 4.—*Induced Tolerance for White Lead*

X119	Pb	4	[6]	Pb	6	[18]	Pb	12	[21]	Pb	16
X120	Pb	4	Died								
X121	Pb	4	Died								
X122	Pb	4	Died								
X123	Pb	4	Died								
X124	Pb	4	[6]	Pb	5	Died					
X125	Pb	4	[6]	Pb	6	[18]	Pb	12	[21]	Pb	16
X126	Pb	4	[6]	Pb	6	[18]	Pb	12	[21]	Pb	16

Pb dosage per day = 0.126 Gm. of commercial white lead by mouth (0.162 Gm. in final series).

This table shows in condensed form the same data embodied in table 3. The unbracketed numbers indicate consecutive days of lead administration; the bracketed numbers, the duration in days of the recovery periods between succeeding periods of lead administration.

days they survived sixteen doses, four times the amount that produces convulsions in all untreated animals and death in one half of them. In this instance each daily dose was 0.126 Gm. of commercial white lead up to the seventy-eighth day of the experiment and 0.162 Gm. of commercial white lead thereafter. Thus, six doses of the larger size were given toward the end of the final sixteen dose series. Five consecutive doses of this magnitude always kill untreated guinea-pigs. The essential data of this experiment are condensed and indicated more clearly in table 4. The history of each animal as to "leading" is shown, the number following each Pb indicating consecutive days of lead administration and the numbers in square brackets, the interpolated free periods.

Animals in which there has been induced a relative tolerance of the type shown by the three survivors of the group just described may henceforth be used as controls in groups of untreated animals with most interesting results. In table 5, for instance, guinea-pig X126 from an earlier series was "leaded" with seven previously untreated animals.

TABLE 5.—*Experimentally Induced Tolerance to the Meningocerebral Manifestations of Poisoning from Commercial White Lead*

Guinea-Pig	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45
X126	630 Pb	Pb	620 Pb	Pb	..	..	..	690 Pb	Pb	Pb	670 Pb	Pb	Pb	Pb	Pb	680 Pb	Pb	Pb	Pb	..	..	..	..	..	..	..	..	Pb	Pb	Pb	Pb	Pb	Pb	Pb	..	..	..	..	745 ..	..
X135	530 Pb	Pb	460 Pb	Pb	† +																																			
X136	560 Pb	Pb	500 Pb	.. +	..	..	..	425 ..	..	..	..	..	..	..	..	..	455 Pb	Pb	Pb	..	..	..	..	..	..	..	..	..	Pb	Pb	Pb	Pb	Pb	Pb	Pb	..	..	..	..	475 ..	..
X137	490 Pb	Pb	445 Pb	.. +	.. +	..	..	320 ..	†																															
X138	680 Pb	..	..	..	..	..	..	650 Pb	Pb	..	..	..	..	..	.. +	..	570 Pb	Pb	Pb +	.	..	..	575 Pb	Pb	Pb	Pb	..	..	..	..	..	..	..	Pb	Pb	Pb	Pb	Pb	Pb	440 ..	†
X139	670 Pb	..	..	..	..	..	..	670 Pb	Pb	..	..	..	..	..	..	..	650 Pb	Pb	Pb	..	..	..	659 Pb	Pb	Pb	Pb	..	..	..	..	..	..	..	Pb	Pb	Pb	Pb	Pb	Pb	Pb	705 Pb	..
X140	475 Pb	..	..	..	..	..	..	460 Pb	Pb	..	..	..	..	..	..	..	425 Pb	Pb	Pb	..	..	..	425 Pb	Pb	Pb	Pb	..	..	..	..	..	..	..	Pb	Pb	Pb	Pb	Pb	Pb	Pb	435 Pb	..
X141	365 Pb	..	..	..	.. +	..	..	375 Pb	Pb	..	..	..	..	..	..	..	330 Pb	Pb	Pb	..	.. +	325 †																			

Pb = 0.171 Gm. of commercial white lead.
The previously treated animal, guinea-pig X126, is utilized as a control in the group.

Although no convulsions resulted in this animal from four, and shortly thereafter from twelve, consecutive doses, the untreated animals showed convulsions from an initial series of three and four doses, the later causing death. In one instance a convulsion followed a single administration. The death of one animal (guinea-pig X141) after the third series of three doses and of another (guinea-pig X138) after a fourth series of six doses is interpreted as indicating that the free periods were too short. Only guinea-pig X136, X139 and X140 in this group acquired a significant degree of tolerance. The gain in weight of the control animal contrasts with the general loss of weight of those receiving lead for the first time, but in the latter there is a definite tendency for the lost weight to be regained if some degree of tolerance is acquired. This is true particularly of guinea-pig X139. One purpose in arranging the dosage for this group was to investigate the rôle played by the convulsions themselves. It seemed possible that certain changes might be induced by the violent convulsions of such a nature as to render the animal less susceptible to future convulsive seizures. By giving only one capsule in the first series and reaching the convulsion producing level of four doses by increments of one only, two animals from this group, guinea-pigs X139 and X140, were made to acquire a high degree of tolerance without at any time having suffered from convulsions. Such evidence as this shows that convulsions are not themselves essential to the acquisition of tolerance to the convulsive manifestations of lead meningo-encephalopathy.

An even more striking test of the acquisition of tolerance can be obtained by using untreated animals as controls in groups made up of those which have been prepared by a graded series of increasing periods of "leading." Such a grouping is shown in table 6. Six guinea-pigs previously treated with lead compounds were combined with two untreated animals and all were given five consecutive daily doses of 0.155 Gm. of lead carbonate. This amount, as has been previously shown, invariably induces a fatal series of convulsions in untreated animals. The six previously exposed to lead had no convulsions and none died. The preparatory administration of lead is shown in the right hand column. This information for guinea-pig X145, for instance, is to be read as follows: Sixty-four capsules of white lead over a period of eight months; a free period of one year; six consecutive daily doses; a rest period of thirty-seven days; ten consecutive daily doses and a final rest period of sixty-two days before starting the period of lead administration detailed in this table. The two untreated animals developed convulsions and died, as was expected. It will be noted that the six animals showing tolerance, as a group, suffered no significant loss of weight.

There is some evidence indicating that, whatever the mechanism of this type of tolerance may be, it persists and is still operative after a long time. In table 7 are condensed the protocols of four guinea-pigs that had received many small doses of white lead over a period of eight

TABLE 6.—*Acquired Tolerance for Lead*

Guinea-Pig	1	2	3	4	5	6	7	8	9	10	11	12	13	Previous "Leading"
X145.....	760 Pb	Pb	Pb	Pb	Pb	...	...	...	...	...	...	...	760 ...	Pb 64 in 8 months [1 year] Pb 6 [37] Pb 10 [62]
X146.....	730 Pb	Pb	Pb	Pb	Pb	...	...	...	...	...	...	...	680 ...	Pb 3 [10] Pb 6 [54]
X148.....	710 Pb	Pb	Pb	Pb	Pb	...	...	...	...	...	...	...	700 ...	Pb 2 [10] Pb 4 [56]
X151.....	770 Pb	Pb	Pb	Pb	Pb	...	...	...	...	...	...	...	770 ...	Pb 3 [22] Pb 5 [34]
X152.....	670 Pb	Pb	Pb	Pb	Pb	...	...	...	...	...	...	...	725 ...	Pb 3 [22] Pb 5 [34]
X157.....	770 Pb	Pb	Pb	Pb	Pb	...	...	...	...	...	...	...	775 ...	Pb 4 [35]
X159.....	850 Pb	Pb	Pb	Pb	Pb +	... +	... +	† +	...	...	...	...	...	None
X160.....	800 Pb	Pb	Pb	Pb	Pb	...	... +	...	...	...	...	...	†	None

Pb = 0.155 Gm. of chemically pure lead carbonate (in previous "leading" various dosages).

This table compares the response of six guinea-pigs previously treated with lead with that of two untreated animals when all are given five 0.155 Gm. doses of lead carbonate on consecutive days. The two controls developed convulsions and died. The six animals prepared by the previous administration of lead showed no convulsions and none of them died.

TABLE 7.—*Persistence of Tolerance to the Meningocerebral Manifestations of Lead Poisoning*

Guinea-Pig	1	2	3	4	5	6	7	8	9	Previous "Leading"
X142.....	715 Pb	Pb	Pb	Pb	Pb	Pb	...	...	715 ...	64 doses in 8 months; no lead for 1 year
X143.....	775 Pb	Pb	Pb	Pb	Pb	Pb	...	...	700 ...	78 doses in 8 months; no lead for 1 year
X144.....	600 Pb	Pb	Pb	Pb	Pb	Pb	...	...	630 ...	67 doses in 8 months; no lead for 1 year
X145.....	715 Pb	Pb	Pb	Pb	Pb	Pb	...	...	600 ...	64 doses in 8 months; no lead for 1 year

Pb = 0.171 Gm. of commercial white lead.

No convulsions appeared in four guinea-pigs which had received no lead for one year but which had been "leaded" before that period. Six consecutive doses of the size given here will cause convulsions and death in untreated animals. Although the record is continued for only nine days, this group was kept under close observation for one month after lead administration ceased and no convulsions occurred.

months in the course of another investigation. They were then put aside for one year When treated, they withstood without convulsions six consecutive daily doses of 0.171 Gm. of white lead, an amount always causing convulsions and death in untreated animals. If further investi-

TABLE 8.—*Convulsions in 100 Per Cent of Group*

Guinea-Pig	1	2	3	4	5	6		14	15	16	17	18	19	20	21		46	47	48	49	50	51	52	53	54	55	56	57	58	59	60
X127	220 Pb	Pb	Pb	Pb	... +	†																									
X128	400 Pb	Pb	Pb	Pb	...	† +																									
X129	225 Pb	Pb	Pb	Pb	† +																										
X130	400 Pb	Pb	Pb	Pb	... +	330 ...	...	570 Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb		415 Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	Pb	...	...	† +

Pb = 0.126 Gm. of white lead in first series.
Pb = 0.162 Gm. of white lead in second and third series.
Such series demonstrate not only the absorption of lead by all the test animals, but also the fact that in our experience no guinea-pigs have been found having such an intrinsic degree of tolerance that convulsions cannot be induced in them.

gations along this line, now under way, confirm this observation such a remarkable retention of acquired tolerance will in itself throw light on the mechanism involved.

Certain objections to the conclusion that this series of experiments demonstrates the acquisition of tolerance are anticipated. The argument must be kept as simple as is possible. A particularly clear cut manifestation of lead poisoning has been selected, the dosage eliciting this in untreated animals determined and, by the interpolation of rest periods between gradual increments in dosage, treated animals have been given four times this amount without the appearance of the test sign. This fact, not tolerance for lead in general and not the mechanism concerned in its production, forms the subject of this report.

Are the results obtained due to failure to absorb lead from the gastro-intestinal tract? The dosage used produced convulsions in all untreated animals and most of those which finally exhibited tolerance had themselves suffered from convulsions during their earlier "leading." We have never found a guinea-pig that did not absorb lead in sufficient amount to produce convulsions if it had never had lead before. By using an initial series of doses of sufficient size every animal in a group may be made to show convulsions. This is illustrated by table 8. Since the borderline between the production of convulsions and death is very narrow there will not be many survivors to develop tolerance if this is done. In this instance a relative degree of tolerance was gained by the sole surviving animal which succumbed to a third series of twelve consecutive doses. If lead is absorbed less easily after the preparatory treatment than before, that is part of the mechanism by which tolerance is developed and, although of the greatest interest and importance, is not part of the demonstration of tolerance itself. That point must receive further investigation.

Are the results obtained due to a selective process, the susceptible animals dying and the more resistant ones remaining to be called tolerant? Since individual differences exist among laboratory animals as among human beings in respect to their susceptibility to lead this type of selection is bound to occur to some extent. It cannot explain the results reported here since no animal has been considered as having acquired a relative tolerance unless it has gained the power of withstanding a greater dosage than not only it, but also any other similar animal, could withstand before treatment. As is indicated by table 8, to which reference has just been made, intrinsic immunity of such a degree that convulsions cannot be induced apparently does not exist in the guinea-pig. Thus, the factor of selection through elimination by death is ruled out.

We believe that the results reported here constitute a demonstration of experimentally induced tolerance to lead poisoning in respect to the meningocerebral manifestations as they occur in the guinea-pig.

THE DETOXICATION OF PUTREFACTIVE PRODUCTS BY THE HUMAN BODY*

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The work of the many investigators on the relation of the liver to blood pressure, especially that of Major [1] and of James, Laughton and McCallum [2] is keeping before our minds the importance of the chemical functions of the liver. Besides these very interesting reactions there are also those of the detoxication of toxic organic compounds, either those naturally produced by bacterial decomposition of waste material in the body or those introduced into the organism in the course of experimental work. It is with the latter reactions that our laboratory has been chiefly interested during the last ten years;[3] in fact, the detoxication reaction involving the acetylation of aminobenzoic acid has already been found to be a very good liver function test, although not as yet developed into a routine clinical method.[4] This fact will be referred to again later on.

According to the teaching of Metchnikoff, a man is as old as his arteries; in other words, the expectation of a man's life is inversely proportional to his blood pressure. According to him, blood pressure of the high tension type as well as practically all the other ills that flesh is heir to seemed to depend on the amount of bacterial decomposition in the gastro-intestinal tract, and of the possible harmful products resulting from this decomposition he considered chiefly those derived from protein material. In fact, he regarded the production of acid through the bacterial decomposition of carbohydrate material as decidedly beneficial, seeing that the acid thus formed inhibited the action of proteolytic organisms which flourish only in a mildly alkaline medium. In the past, the work carried on at our laboratory has been largely directed along lines of this nature. Thus, we have been interested in studying these various putrefactive products both as regards their method of formation and their quantitative estimation, and we have given particular attention to the methods by which various toxic substances are detoxicated or

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* From the chemical research laboratory of Fordham University.

1. Major, R. H.: Am. J. M. Sc. **170**:228 (Aug.) 1925.

2. James, A. A.; Laughton, N. B., and McCallum, A. B.: Science **62**:181, 1925.

3. Sherwin, C. P.: Physiological Rev. **2**:238 (April) 1922.

4. Vesell, Harry; and Sherwin, C. P.: Testing of Liver Function; Detoxication by Liver, Arch. Int. Med. **37**:257 (Feb.) 1926.

rendered innocuous by the animal organism. By far the best known putrefactive products derived from protein decomposition in the gastrointestinal tract are indol, skatol and phenol. Of these indol is the most notorious; some of it is detoxicated in the animal or human body by its chemical combination with acid potassium sulphate, the resulting compound being known as indican, which is then excreted in the urine. The unaltered and uncombined fraction of the indol is excreted in the feces, and is partly responsible for the unpleasant odor of fecal discharges. Under the heading indican one may read literally thousands of pages of clinical, chemical and physiologic literature. If not directly the cause of insomnia, melancholia, chorea, various kinds of insanity, and several other less well defined constitutional disturbances, it is at least certain that indican has actually been found in large amounts in the urine in a majority of such cases by different investigators at various times. We have shown in a previous article [5] that the accepted clinical methods for determining indican in the urine, such as the methods of Obermayer or of Jolles, are not only not quantitative but give no results that are even comparable under like experimental conditions. What we have said for the determination of urinary indican holds as well for the corresponding compound of skatol, but to a far less extent for phenol. These conclusions were drawn only after human beings as well as rabbits had been fed several doses of indol, skatol and phenol, and the accepted clinical methods of determining these substances had been checked against the increased output of ethereal sulphates and of glycuronic acid, which afford a more accurate although less convenient index of the amounts of the substances in question. Besides this, we found that as much as 50 mg. of skatol or of indol might be ingested by an adult human being without any untoward results, but that the ingestion of more than this quantity produced the typical symptoms met with in cases of marked constipation, such as nausea, loss of appetite, headache, melancholia and sleeplessness. Vomiting was prevented by coating the gelatin capsules with salicin so that the contents might not be loosed in the stomach, but rather in the intestine.

It must be borne in mind that from a chemical standpoint there are two varieties of putrefaction products, those containing nitrogen and those containing no nitrogen. The nitrogenous putrefaction products are formed by the action of certain bacteria which remove carbon dioxide from the acid group of the protein derivatives present in the gastrointestinal tract, and compounds are thus formed known chemically as amines which are of particular physiologic interest on account of their reputed marked toxicity. In the formation of the non-nitrogenous putrefaction products, nitrogen is first removed from the amino-acids of the

5. Novello, N. J.; Wolf, M., and Sherwin, C. P.: Am. J. M. Sc. **170**:888 (Dec.) 1925.

decomposing protein molecule, and a compound is left behind which is acidic in character and which contains only carbon, hydrogen and oxygen. This type of compound is in general much less harmful from a physiologic standpoint than the nitrogen containing compounds. The work done at our laboratory on the latter compounds has been to prepare a number of these putrefaction products in the laboratory and to feed them in varying amounts, then to study not only their relative toxicity but also the method by which they might be detoxicated.

Taking human beings as subjects, we administered to them varying doses of the chemically pure putrefaction products which we had previously prepared in the laboratory. These substances were administered for the most part on a fairly empty stomach or just before the evening meal, this being the heaviest meal of the day. The protein decomposition products of acid character were usually ingested in the form of a

Fate of Some Protein Putrefactive Products in the Human Body

Name of Compound Fed	Fed in 24 Hours	Excreted Unchanged	Oxidized	Combined With	Excreted in Urine Chiefly in Form of	Percentage of Total Dose Recovered in Urine
Nitrogen-free substances	Grams					
Benzoic acid	20	Partly	No	Glycocoll	Hippuric acid	80
Phenylacetic acid	16	Partly	No	Glutamine	Phenylacetylglutamine	50
Phenylpropionic acid	12	Partly	Yes	Glycocoll	Hippuric acid	90
Parahydroxybenzoic acid	20	Entirely	No	.....	Unchanged	70
Parahydroxyphenylacetic acid	8	Entirely	No	.....	Unchanged	75
Parahydroxyphenylpropionic acid	16	Partly	Yes	.....	Unchanged	65
Nitrogen containing substances						
Indolformic acid	6	Entirely	No	.....	Unchanged	80
Indolacetic acid	4	Entirely	No	.....	Unchanged	90
Phenylethylamine	1	?	Yes	.....	Phenylacetic acid	50
Tyramine	1	?	Yes	.....	Parahydroxyphenylacetic acid	60
Indolethylamine	1	?	Yes	.....	Indolacetic acid	60

water solution of the sodium salt prepared by adding the substance to a solution of sodium carbonate until neutrality to litmus was obtained. The nitrogenous substances, on the other hand, were easily dissolved in water by adding at the same time a little dilute inorganic acid such as hydrochloric acid, thereby forming the soluble salt of the amine. It was not desired to feed the material in capsules because thus all the substance would be deposited either in the stomach or intestine at one time and in a very localized region, thereby more than likely causing a local irritation of the mucous membrane and simply hindering the rapid absorption of the substance. If ingested as solution, the substance would be gradually liberated by the acid gastric juice if it were in an alkaline solution, and would undergo much the same process in the

intestine if in acid combination. The urine was voided immediately after ingestion of a dose of the substance and then all the urine was collected in twenty-four hour periods. The evaporated urine was then acidified, extracted with some organic solvent such as alcohol, ether or ethyl acetate. The feces were not examined for the unchanged compound, as the dosage was small and the compound should have been largely absorbed from the gastro-intestinal tract; besides, we were chiefly interested in the process by which the human body detoxicates these poisonous compounds.

In the accompanying table may be seen the names as well as the relative toxicity of the compounds fed. The figure in the left hand side of the table shows the maximum dosage that the human body is able to dispose of in the course of twenty-four hours when the total amount is divided into equal doses and ingested at six hour intervals.

COMMENT

The amino-acids that are chiefly concerned in the putrefactive decomposition of proteins or, in other words, those components of the protein molecule from which are derived the most undesirable putrefactive products are tryptophane, tyrosine and phenylalanine. Phenylalanine, after losing its nitrogen containing amino group according to the first set of reactions forms phenylpropionic acid, then phenylacetic acid, and lastly benzoic acid, by losing respectively one, two and three carbon atoms through the action of bacterial decomposition. Tyrosine, which is parahydroxyphenylalanine, in a similar manner forms, according to these reactions, parahydroxyphenylpropionic acid, parahydroxyphenylacetic acid, and parahydroxybenzoic acid. Tryptophane forms in the same way indolpropionic acid, indolacetic acid, and indolformic acid, when the acid joined to the indol has respectively three, two, and one carbon atom. We were unable to prepare indolpropionic acid in sufficient amounts for the experimental work so were limited to the use of indolacetic and indolformic acid.

The scheme for the detoxication of these nonnitrogenous compounds is in general the same in the human as in the animal body. There is first an attempt on the part of the organism to oxidize or burn up the foreign molecule, but as each of these compounds is a coal tar derivative it contains a benzene nucleus which is highly resistant to the oxidative mechanism, so only a part of the molecule is burned, that is, the aliphatic part or "side-chain"; then the oxidation ceases. For instance, phenylpropionic acid loses two carbon atoms and is thus changed into benzoic acid. If the compound is entirely nontoxic it is excreted free in the urine as the sodium salt. The remainder of these acids are to some degree toxic and are therefore detoxicated by joining them to glycine or amino-acetic acid, with the exception of phenylacetic acid, which is joined to glutamine. It is an interesting fact that the human body, like

the animal, can synthesize one of the protein constituents (the glycine) out of refuse material (the urea nitrogen) when it needs the glycine for detoxication purposes, but the human, *unlike* the animal, can also synthesize a second amino-acid (glutamine) from the same source for defensive purposes.[6]

While considerable is known regarding the non-nitrogenous protein decomposition products in the body, little is known as to the fate of the nitrogen containing molecules. We know, however, that they are much more toxic than the other non-nitrogenous compounds. We therefore employed the amines derived from the same three amino-acids already mentioned, namely, tryptophane, phenylalanine and tyrosine; these amines are called, respectively, indolethylamine, phenylethylamine and tyramine. We found that, as was expected, the compounds were much more toxic than the non-nitrogenous protein derivatives, but in the long run they were by no means as toxic as had ordinarily been thought. In each of these compounds we find the same coal tar or aromatic nucleus with a side chain of two carbon atoms and a nitrogen atom. In the detoxication of these basic compounds the first step seems to be the splitting off of the nitrogen of the amino group and the conversion of the compound into the corresponding alcohol which after oxidation is finally converted into a non-nitrogenous compound of an acid nature, in this case into an acetic acid derivative, namely, indolacetic or else phenylacetic acid. This reduces the toxicity to about 3 per cent of the corresponding nitrogenous compound.

The cite or location of this detoxication process in the body is a question that has aroused considerable interest and has called forth several different hypotheses. The work of Kingsbury[7] has shown that benzoic acid is largely conjugated with glycocoll by the kidney in a normal person but that in the case of lowered kidney function the work of detoxication may to a large degree be taken over by the liver. In our own laboratory we[8] have found that certain aniline derivatives are detoxicated in the human body by joining them with acetic acid. This is true only in the case of normal human beings, and the reaction is very limited in the case of persons with damaged livers. In fact, this is so much the case that the extent of acetylation after the ingestion of one of these aniline-like compounds seems to be a good indication of the efficiency of hepatic function. Koessler and Hanke[9] have shown in their work on histamine that the gastro-intestinal wall very likely is the seat of some detoxicating mechanism, while other experimenters, after

6. Sherwin, C. P.; Wolf, M., and Wolf, W.: J. Biol. Chem. **37**:113 (Jan.) 1919. Shiple, G. J., and Sherwin, C. P.: J. Am. Chem. Soc. **44**:618, 1922.

7. Kingsbury, F. B., and Bell, E. T.: J. Biol. Chem. **21**:297, 1915.

8. Muenzen, J. B.; Cerecedo, L. R., and Sherwin, C. P.: J. Biol. Chem. **67**: 469, 1926.

9. Koessler, K. K., and Hanke, M. T.: J. Biol. Chem. **59**:889 (April) 1924.

passing blood through the surviving livers of dogs noted that the aromatic amines (of the type we have used in this experiment) if dissolved in the ingoing blood could be accounted for after passing through the liver as the corresponding acid. There are therefore three possible or even probable places where this detoxication takes place—the liver, the kidney, and the wall of the gastro-intestinal tract. It seems most probable, however, that the two latter named possibilities are only of minor importance, thus leaving the liver as the most probable site of general detoxication.

In consideration of the relative toxicity of these compounds we may safely say that their importance from this standpoint has been greatly exaggerated. For example, when we consider that the average daily output of benzoic acid (in the combined form of hippuric acid) amounts to but 0.3-0.6 Gm. per day, and that perhaps most of this is of endogenous origin, we must conclude that this putrefactive product is of only moderate importance. The quantity of the other non-nitrogenous constituents of the urine is negligible. Even in the case of persons suffering from severe autointoxication, many liters of the urine must be collected before even traces of the other compounds of this type, such as phenylacetic acid, parahydroxyphenylacetic acid, phenylpropionic acid and parahydroxybenzoic acid, can be found. Large doses such as were administered in the course of this experiment did not lead to the classical symptoms supposedly due to the overproduction of putrefactive products in the intestine, symptoms such as irritability, loss of appetite and sleeplessness. On the contrary, there appeared an increased appetite and general slowing up of cerebral function, along with a feeling of drowsiness.

The toxicity of the nitrogen containing products of protein decomposition is, however, a different question. These are from twenty to one hundred times as toxic as the non-nitrogenous compounds. They produce much more of a general reaction, usually a feeling of nausea with temporary loss of appetite, high nervous tension and sleeplessness, followed usually in a short time by a feeling of impending evil and always by a severe diarrhea. There is a slight elevation of temperature and increased pulse rate, with rise in arterial tension. It seems to us, however, that even the importance of this type of putrefactive product has been somewhat overestimated. Its toxicity depends chiefly on the rapidity of its absorption as compared to the considerable period of time necessary for its detoxication.

The human body it would seem is equipped with a chemical defense mechanism that is capable of detoxicating the various types of putrefactive products formed within the intestines, and at the same time is able to cope with larger quantities of these products than are normally present within the intestine. The human body follows in general the same line of chemical defense as does the lower animal, that is, the destruction

of an organic poison by means either of oxidation or reduction. In case these means fail, the compound is detoxicated by combining it with another compound or organic radical. Several of these compounds used in detoxication, such as glycocoll, glutamine, acetic acid and glycuronic acid, although not stored in the body for emergency purposes, can be synthesized in considerable quantities when necessary for this purpose. The human body is different from that of the lower animals in that it employs glutamine in one of its detoxication processes—a compound used by none of the lower animals so far investigated.

SUMMARY AND CONCLUSIONS

1. There are two general classes of decomposition products formed from protein in the lower intestine due to bacterial action, namely, the non-nitrogenous and the nitrogenous or amino derivatives.

2. We prepared the principal non-nitrogenous putrefactive products of the three amino acids, phenylalanine, tyrosine and tryptophane, namely, benzoic acid, phenylacetic acid, phenylpropionic acid, parahydroxybenzoic acid, parahydroxyphenylacetic acid, parahydroxyphenylpropionic acid, indolformic acid and indolacetic acid.

3. These non-nitrogenous putrefactive products were fed to human beings in order to determine their toxicity; then the urine was examined in order to identify the detoxication product and hence the method of detoxication by the body.

4. Phenylpropionic acid was oxidized to benzoic acid, which was then combined with glycocoll and excreted as hippuric acid. Phenylacetic acid was excreted in combination with glutamine. The other acids were excreted uncombined. In the table is found the maximum dosage of each, also the amount recovered from the urine.

5. Of the nitrogenous or amino derivatives of the foregoing amino acids, namely, phenylethylamine, tyramine and indolethylamine, all three were prepared and fed in 1 Gm. amounts during a period of twenty-four hours.

6. These amino compounds proved much more toxic than the non-nitrogenous substances. They were detoxicated by the body by splitting off the nitrogen, thus converting them into the acidic compounds of the type mentioned above.

7. The cite of these detoxication reactions would appear to be chiefly the liver, but to some extent this function may be performed by the kidney or the gastro-intestinal wall.

8. The human body is apparently provided with a chemical defense mechanism nonspecific in character which is more than adequate for the detoxication of the small amount of putrefactive products normally produced in the human intestine by the action of putrefactive bacteria on unabsorbed protein material.

DIABETES

A STATISTICAL STUDY OF ONE THOUSAND CASES*

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CLEVELAND

Statistical studies of a large series of individual cases of any disease offer considerable information, especially in regard to phenomena of its various stages, the incidence of different phases and their interrelationship. In particular, such a review enables one to see his mistakes and gives an opportunity to alter management accordingly. For these reasons I am offering this review of 1,000 consecutive cases of diabetes which have been under observation during the last five years. This study covers the period from March 1, 1921, through August, 1925, when the one-thousandth case was seen. The total number of patients admitted to the Cleveland Clinic during this period was 55,939; thus, the incidence of diabetes to all other diseases among our patients is nearly 1.8 per cent.

AGE AND SEX INCIDENCE

Chart 1 shows the distribution of these cases according to sex and in different age decades. It will be noted that there is a strikingly increased incidence in the fifth, sixth and seventh decades, but that there is no significant difference in the sex incidence in any decade. It is not strange that, as middle age approaches and is passed, the organism shows some signs of imperfect or markedly diminished carbohydrate metabolism, just as at this period the beginning failure of other functions is shown by the development of myocarditis, chronic nephritis and hypertension in greater frequency than in earlier years. That the development of diabetes in later life is part of the general degenerative process which affects sometimes one and sometimes another organ, according to the relative degrees of resistance, is indicated by the fact that when diabetes is inaugurated at this time it is usually of a milder degree than when it is of earlier onset.

In chart 2 I have summarized the incidence of diabetes by decades, according to the data of ten different authors, as cited by Joslin,[1] and in table 1 are given data from the seven observers whose work he reviews. A more specific classification by individual years from 1 to 30 has been prepared in table 2, which emphasizes the fact that diabetes occurs in the earliest years, although the percentage of incidence increases when the totals for each decade are considered.

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* From the Medical Division, Cleveland Clinic.

1. Joslin, E. P.: The Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1923, p. 123.

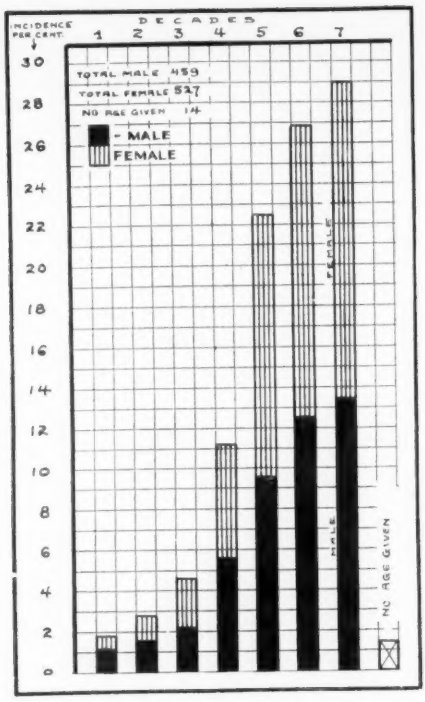

Chart 1.—The sex and age incidence of diabetes (from author's series of 1,000 cases).

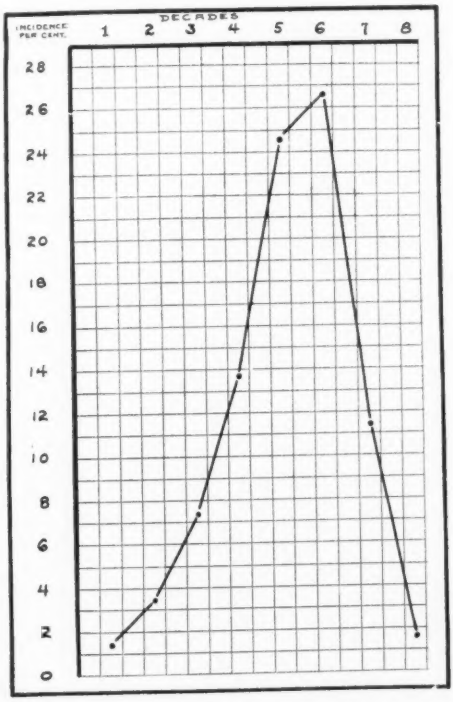

Chart 2.—The average incidence of diabetes in different age decades (compiled from the literature).

TABLE 1.—*Incidence of Diabetes According to Age Decades (Compiled from the Literature)*

	Decades								
	I	II	III	IV	V	VI	VII	VIII	
Frerichs	1	7	10	18	25	26	11	1	
Seegen	0.5	3	16	16	24	30	10	0.5	
Grube	....	1.7	2.8	11.2	23.1	39.5	18.1	3.4	
Schmitz	0.83	4.1	9.3	17.3	22.3	32.6	10	3.3	
Pavy	0.58	4.19	7.13	16.4	24.9	30.7	13.4	2.5	
Külz	1	3	4.6	17.2	36	26.8	9.2	0.1	
Von Noorden	....	0.43	2.4	10	21	17.7	4	0.4	Light cases
Von Noorden	1.43	2.43	6	9.57	12.5	11	2.1	...	Severe and moderately severe

Umber reports eleven children in his last series of 200 cases of diabetes.

TABLE 2.—*Incidence of Diabetes in the First Three Age Decades (From Author's Study of One Thousand Cases of Diabetes)*

Year	Number of Male Patients	Number of Female Patients	Total Number of Patients	Percentage of 1,000 Cases
1	1	1	2	0.2
2	2	1	3	0.3
3	1	..	1	0.1
4	..	1	1	0.1
5	1	1	2	0.2
6	..	1	1	0.1
7	2	..	2	0.2
8	..	1	1	0.1
9	2	1	3	0.3
10	2	..	2	0.2
11	3	1	4	0.4
12	1	..	1	0.1
13	1	..	1	0.1
14	1	1	2	0.2
15	4	..	4	0.4
16	2	..	2	0.2
17	1	3	4	0.4
18	2	4	6	0.6
19	..	1	1	0.1
20	1	2	3	0.3
21	..	4	4	0.4
22	5	..	5	0.5
23	..	3	3	0.3
24	..	1	1	0.1
25	..	4	4	0.4
26	3	5	8	0.8
27	3	5	8	0.8
28	6	..	6	0.6
29	2	1	3	0.3
30	1	1	2	0.2

TABLE 3.—*The Heredity Factor in the Incidence of Diabetes (After Joslin*)*

Author	Date of Compilation	Number of Cases	Percentage of Cases with Hereditary or Familial History of Diabetes	
Grube	....	...	8.0	
Frerichs	....	400	9.8	
Seegen	....	...	14.0	
Schmitz	....	...	20.0	
Külz	....	692	21.6	
Williamson	....	500	22.0	
Bouchard	....	...	25.0	
Naunyn	1905	398	17.0	
Von Noorden	1917	...	25.4	Hereditary 18.5 Familial 6.9
Joslin	1923	2,800	21.0	Hereditary 15.0 Familial 7.0

* Joslin, E. P.: The Treatment of Diabetes Mellitus, p. 128.

HEREDITY

The rôle of heredity in the production of diabetes is mentioned by all writers on this subject. In table 3 I have compiled the observations of various observers in order to compare my own results, as given in table 4, with theirs. The percentages given in this list make one feel that heredity must play some part in the incidence of diabetes.

While the percentage of diabetic cases in which one can trace either a familial or a hereditary connection is fairly large, nevertheless it would seem that the factor of environment plays a more important rôle in this group of cases. In a large percentage of cases in this group, the patients were either obese or at least overweight. We do not know the state of

TABLE 4.—*The Heredity Factor in the Incidence of Diabetes (From Author's Study of One Thousand Cases of Diabetes*

	Cases	Percentage of Total Series
Familial history	51	
Hereditary history	46	
Total	97	9.7

TABLE 5.—*Blood Sugar in Nine Hundred and Thirty-Three Cases of Diabetes on Admission (From Author's Study of One Thousand Cases of Diabetes)*

Blood Sugar, Mg. per 100 Cc.	Number of Cases	Blood Sugar, Mg. per 100 Cc.	Number of Cases
120	51	400	57
150	179	450	33
200	203	500	25
250	138	600	15
300	119	700	12
350	101		

the pancreas at birth, since of course systematic data from personal observations are lacking on this point; so definite conclusions cannot be drawn. Moreover, in families in which there is a familial or hereditary history of diabetes, we do not know how many subjects do not develop diabetes, regardless of their habits, and what is the proportion of these to those who do develop diabetes. Family histories that offer a striking picture of the incidence of diabetes in several generations have been reported in the literature. But such reports are rare, and diabetes itself has such a high incidence that if heredity is an important factor, a closer relationship should be established than has thus far been done. The important points are that, whatever the familial or hereditary incidence of diabetes, if one lives moderately and stays thin, diabetes will not develop, and that, on the other hand, obesity and overindulgence often lead to diabetes even when there is no hereditary history of the disease.

BLOOD SUGAR CONTENT AND GLYCOSURIA

In this series of diabetic patients, the blood sugar on admission varied from 120 to more than 900 mg. per hundred cubic centimeters of blood. The lower figures were found either in early cases or in cases in which the blood sugar was being controlled by proper diet or by diet plus insulin. Table 5 shows the distribution of the cases in this series at the different blood sugar levels. It will be noted that in a large majority of these cases the blood sugar content ranged from 150 to 350 mg. per hundred cubic centimeters, but, while higher figures occur less frequently, they are far from being exceptional.

TABLE 6.—*Blood Sugar Without Glycosuria in Two Hundred Cases of Diabetes on Admission (From Author's Study of One Thousand Cases of Diabetes)*

Blood Sugar, Mg. per 100 Cc.	Number of Cases	Blood Sugar, Mg. per 100 Cc.	Number of Cases
120	20	200	10
130	14	210	4
140	33	220	8
150	31	230	7
160	24	260	4
170	18	270	1
180	15	310	1
190	10		

TABLE 7.—*Blood Sugar with Glycosuria in Three Hundred and Ninety-Two Cases of Diabetes on Admission (From Author's Study of One Thousand Cases of Diabetes)*

Blood Sugar, Mg. per 100 Cc.	Number of Cases	Blood Sugar, Mg. per 100 Cc.	Number of Cases	Blood Sugar, Mg. per 100 Cc.	Number of Cases
120	8	230	17	330	14
130	4	240	11	340	15
140	7	250	14	350	14
150	15	260	12	360	5
160	8	270	16	370	5
170	12	280	18	380	10
180	13	290	16	390	7
190	11	300	16	400	6
200	15	310	9	500	35
210	15	320	17	600	19
220	8				

Table 6 offers us an instructive study of the relationship of glycosuria to hyperglycemia in cases of diabetes. The highest blood sugar figure in which glycosuria was not present was 310 mg. per hundred cubic centimeters. This table shows clearly that in these cases of diabetes the permeability of the kidney to sugar certainly is lessened, the threshold raised.

Table 7 shows the incidence of glycosuria at the different blood sugar levels.

Some of the highest blood sugar values that I have seen reported in the literature are listed in table 8. The highest blood sugar content seen in any of my patients on admission was in the case of a man,

aged 47, a bricklayer, who had had all the classic signs of diabetes for nearly a year but had had no treatment. He was losing weight and strength daily but did not give up work, and when he came to me his blood sugar was 908 mg. per hundred cubic centimeters, and he had a glycosuria of 10 per cent. Some of the other high blood sugar values observed in patients on admission were 732, 652, 696, 600, 778 (coma), 810 (coma), 696, 638, 652, 810 and 732. Such a list seems surprising, but it should be remembered that while an extremely high blood sugar content proves the presence of diabetes, it does not always produce some of the usual signs, such as dryness of the mouth and tongue, extreme thirst, blurring of vision and loss of weight. Often, therefore, persons with a high blood sugar content are comparatively comfortable, with the

TABLE 8.—*Highest Blood Sugar Values in Diabetic Patients Reported by Various Observers (Compiled from the Literature)*

Author	Blood Sugar, Mg. per 100 Cc.	Patient's Condition
Pitfield, R. L. (M. J. & Record **120**: 433, 1924)	1,700	Coma
Joslin, E. P. (Treatment of Diabetes Mellitus, p. 173)	1,370	Coma
Foster, N. B. (J. A. M. A. **84**: 719, 1925)	1,260	Coma
	890	Coma
Paddock, B. W. (J. A. M. A. **82**: 1855, 1924)	1,040	Coma
Liefmann and Stern (cited by Bang, I.: Der Blutzucker, p. 135)	1,010	Coma
Weiland, W. (Klin. Wchnschr. **2**: 736, 1923)	940	Coma
Chapin and Myers (Am. J. Dis. Child. **18**: 555, 1919)	790	.....
Author's cases	908	.....
	910	.....
	810	Coma
	778	Coma
	732	.....
	732	.....

exception of thirst and frequency of urination, and are unconscious of their true condition.

The highest blood sugar figure that I have ever obtained was in the case of a patient in coma in which, immediately after the intravenous administration of insulin and glucose, the blood sugar content was 2,610 mg. per hundred cubic centimeters, having been 405 mg. per hundred cubic centimeters immediately before the administration. On another occasion in the same case, the blood sugar was 1,108 mg. per hundred cubic centimeters following, and 79 mg. per hundred cubic centimeters immediately before, intravenous medication. This patient has had three attacks of coma, each due to an indiscretion in diet; yet she is in better health and more active today than she has been for many years, as a result of the continued use of large doses of insulin.

TREATMENT WITH INSULIN

There seems to be a general impression on the part of the public that insulin treatment is to be avoided if possible, for it is the prevalent opinion that if insulin is taken once, its use must be continued indefinitely

TABLE 9.—*Lasting Effects of Insulin in Treatment of Diabetes as Indicated by Blood Sugar Determinations at Varying Periods After Its Discontinuance (From Author's Study of One Thousand Cases of Diabetes)* *

Age of Patient	Duration of Diabetes	Duration of Insulin Treatment	Period Since Discontinuance of Insulin	Blood Sugar Content When Insulin Was Started	Present Blood Sugar Content
18	3 weeks	31 months	2 months	261	110
23	1 year	6 months	2 months	250	97
26	1 year	4 months	2 months	400	134
28	Recent	5 months	11 months	241	89
32	1 month	45 days	1 month	400	82
38	1 year	15 days	2 months	344	123
39	1 year	16 days	4 months	340	161
40	8 years	75 days	7 months	266	155
42	2 months	60 days	10 months	154	132
43	3 years	16 months	1 month	323	100
43	1 month	5 months	11 months	238	111
44	4 months	4 days	25 months	297	107
44	3 years	17 months	1 month	410	79
44	2 years	16 days	5 months	261	126
45	8-9 years	7 days	34 months	206	172
45	Recent	14 days	22 months	275	138
45	1 month	60 days	5 months	428	106
46	2 years	7 days	21 months	319	104
47	2 years	7 days	23 months	176	90
47	4 years	12 days	4 months	400	110
49	Recent	2 days	14 months	176	125
50	1 year	2 days	17 months	200	76
50	6 years	5 days	23 months	353	133
50	1 year	13 days	23 months	241	130
53	6 weeks	8 days	11 months	353	179
53	2 years	5 days	21 months	227	106
53	Recent	14 days	3 months	280	142
53	1 year	1 month	21 months	202	125
53	Recent	6 days	33 months	200	129
54	Recent	12 days	13 months	384	111
55	2 years	8 days	24 months	467	105
55	6 months	6 days	17 months	163	87
55	2½ months	3 days	5 months	440	60
55	Recent	12 days	25 months	282	80
55	3-4 months	40 days	1 month	169	98
56	1 year	14 days	7 months	454	116
56	1 year	15 days	3 months	394	165
56	4 years	6 days	7 months	167	128
57	4-5 years	14 days	17 months	234	131
57	10-12 years	12 days	18 months	227	117
58	2 years	6 months	13 months	243	122
59	7-9 years	10 days	19 months	294	152
60	Recent	6 days	17 months	182	133
61	3 years	2 days	34 months	194	113
61	7 years	2 days	34 months	232	117
61	5 months	8 days	3 months	344	168
61	1 year	12 days	23 months	333	129
62	Recent	5 days	15 months	243	98
62	1 year	30 days	13 months	222	118
62	1½ years	12 days	12 months	258	112
62	1 year	2 months	1 month	275	98
65	2 years	3 days	11 months	208	126
65	4 years	11 months	12 months	344	145
66	15 years	30 months	6 months	190	167
68	5 years	11 days	23 months	221	131
70	1 month	5 days	16 months	370	85
74	1 year	5 days	18 months	344	156
79	12 years	2 days	5 months	333	116

* Arranged in order of ages of patients.

This is an erroneous conception. It is advantageous to begin treatment with insulin just as soon as the diagnosis of diabetes is established, thus shortening the time the patient must spend at the hospital—an economic advantage both for the patient and for the physician or clinic. Why should one spend a week or ten days on a fasting or a low diet in an attempt to bring a marked hyperglycemia to a normal level if the same end can be accomplished in from twenty-four to forty-eight hours

TABLE 10.—*Lasting Effects of Insulin in Treatment of Diabetes as Indicated by Blood Sugar Determinations at Varying Periods After Its Discontinuance (From Author's Study of One Thousand Cases of Diabetes)* *

Duration of Diabetes	Age of Patient	Duration of Insulin Treatment	Period Since Discontinuance of Insulin	Blood Sugar Content When Insulin Was Started	Present Blood Sugar Content
Recent	49	2 days	14 months	176	125
Recent	62	5 days	15 months	243	98
Recent	28	5 months	11 months	241	89
Recent	53	14 days	3 months	280	142
Recent	54	12 days	13 months	384	111
Recent	60	6 days	17 months	182	133
Recent	53	6 days	33 months	200	129
Recent	45	14 days	22 months	275	138
Recent	55	12 days	25 months	282	80
3 weeks	18	31 months	2 months	261	110
6 weeks	53	8 days	11 months	353	179
1 month	45	60 days	5 months	428	106
1 month	43	5 months	11 months	238	111
1 month	70	5 days	16 months	370	85
1 month	32	45 days	1 month	400	82
2 months	42	60 days	10 months	154	132
2½ months	55	30 days	5 months	440	60
3-4 months	55	40 days	1 month	169	98
4 months	44	4 days	25 months	297	107
5 months	61	8 days	3 months	344	168
6 months	55	6 days	17 months	163	87
1 year	23	6 months	2 months	250	97
1 year	56	14 days	7 months	454	116
1 year	61	12 days	23 months	333	129
1 year	62	30 days	13 months	222	118
1 year	56	15 days	3 months	394	165
1 year	38	15 days	2 months	344	123
1 year	39	16 days	4 months	310	161
1 year	53	1 month	21 months	292	125
1 year	62	2 months	1 month	275	98
1 year	50	2 days	17 months	290	76
1 year	74	5 days	18 months	344	156
1 year	26	4 months	2 months	400	134
1 year	50	13 days	23 months	241	130
1½ years	62	12 days	12 months	258	112
2 years	58	6 months	13 months	243	122
2 years	47	7 days	23 months	176	90
2 years	65	3 days	11 months	208	126
2 years	44	16 days	5 months	261	126
2 years	46	7 days	21 months	319	103
2 years	55	8 days	24 months	467	106
2 years	53	5 days	21 months	227	106
3 years	43	16 months	1 month	323	100
3 years	44	17 months	1 month	410	79
3 years	61	2 days	34 months	194	113
4 years	65	11 months	12 months	344	145
4 years	56	6 days	7 months	167	128
4 years	47	12 days	4 months	400	110
4-5 years	57	14 days	17 months	234	131
5 years	68	11 days	23 months	221	131
6 years	50	5 days	23 months	353	133
7 years	61	2 days	34 months	232	117
7-9 years	59	10 days	19 months	294	152
8 years	40	75 days	7 months	266	135
8-9 years	45	7 days	34 months	206	172
10-12 years	57	12 days	18 months	344	156
12 years	70	2 days	5 months	333	116
15 years	66	20 months	6 months	190	167

* Arranged in order of duration of diabetes.

by means of insulin with a fairly liberal diet? The essential requirements in the treatment of diabetic patients may be briefly summarized as follows: 1. The blood sugar must be brought to, or near, the normal. 2. It must be determined whether or not a comfortable, regulated diet alone will suffice to keep the blood sugar normal. 3. If a sufficient diet alone will not hold the blood sugar in check, then it must be determined how many units of insulin a day are required and how they should be

TABLE 11.—*Lasting Effects of Insulin in Treatment of Diabetes as Indicated by Blood Sugar Determinations at Varying Periods After Its Discontinuance (From Author's Study of One Thousand Cases of Diabetes)* *

Period Since Discontinuance of Insulin	Blood Sugar Content When Insulin Was Started	Present Blood Sugar Content	Age of Patient	Duration of Diabetes	Duration of Insulin Treatment
1 month	323	100	43	3 years	16 months
1 month	410	79	44	3 years	17 months
1 month	275	98	62	1 year	2 months
1 month	400	82	32	1 month	45 days
1 month	169	98	55	3-4 months	40 days
2 months	250	97	23	1 year	6 months
2 months	344	123	38	1 year	15 days
2 months	400	134	26	1 year	4 months
2 months	261	110	18	3 weeks	31 months
3 months	344	168	61	5 months	8 days
3 months	394	165	56	1 year	15 days
3 months	280	142	53	Recent	14 days
4 months	340	161	39	1 year	16 days
4 months	400	110	47	4 years	12 days
5 months	428	106	45	1 month	60 days
5 months	261	126	44	2 years	16 days
5 months	440	60	55	2½ months	30 days
5 months	333	116	79	12 years	2 days
6 months	190	167	66	15 years	20 months
7 months	454	116	56	1 year	14 days
7 months	167	128	56	4 years	6 days
7 months	266	155	40	8 years	75 days
10 months	154	132	42	2 months	60 days
11 months	241	80	28	Recent	6 months
11 months	208	126	65	2 years	3 days
11 months	238	111	43	1 month	5 months
11 months	353	179	53	6 weeks	8 days
12 months	258	112	62	1½ years	12 days
12 months	344	145	65	4 years	11 months
13 months	243	122	58	2 years	6 months
13 months	222	118	62	1 year	30 days
13 months	384	111	54	Recent	12 days
14 months	176	125	49	Recent	2 days
15 months	243	98	62	Recent	5 days
16 months	370	85	70	1 month	5 days
17 months	182	133	60	Recent	6 days
17 months	163	87	55	6 months	6 adys
17 months	234	131	57	4-5 years	14 days
17 months	280	76	50	1 year	2 days
18 months	344	156	74	1 year	5 days
18 months	227	117	57	10-12 years	12 days
19 months	294	152	69	7-9 years	10 days
21 months	319	104	46	2 years	7 days
21 months	292	125	53	1 year	1 month
21 months	227	106	53	2 years	5 days
22 months	275	138	45	Recent	14 days
23 months	333	120	61	1 year	12 days
23 months	176	90	47	2 years	7 days
23 months	221	131	68	5 years	11 days
23 months	353	133	50	6 years	5 days
23 months	241	130	50	1 year	13 days
24 months	467	105	55	2 years	8 days
25 months	297	107	44	4 months	4 days
25 months	282	80	55	Recent	12 days
33 months	200	129	53	Recent	6 days
34 months	194	113	61	3 years	2 days
34 months	232	117	61	7 years	2 days
34 months	206	172	45	8-9 years	7 days

* Arranged in order of periods since discontinuance of insulin.

distributed in relation to the diet. 4. The patient must be taught the essential diabetic diet, and, if insulin is required, how to administer it to himself.

It has been generally stated that in children one is not able to cut down the insulin dosage, but rather that this has to be increased. This is in accordance with my own experience. The limits of safety for a child are much narrower than for adults, and a good clinical result is

much more easily spoiled. On the other hand, in adults there are many cases in which in time the insulin can be discontinued, the patient continuing to be well and keeping a normal blood sugar on diet alone. In tables 9, 10 and 11 the results of the administration of insulin are summarized in a series of cases in which the period of administration varied from a few days to almost three years. This series disproves the belief on the part of the public that insulin once used must be continued for life.

The rapidity with which the blood sugar can be reduced is well illustrated by the case of a young man, aged 22, whom I first saw on June 24, 1925. For two months he had had the classic symptoms of diabetes, but glycosuria was first discovered four days before I saw him; he had not consulted any physician before that time. The blood

TABLE 12.—*Record of Patient (Chart 3)*

Date, 1925	Blood Sugar, Mg. per 100 Cc.				Insulin Dosage in Units				Diet
	8 a.m.	12 m.	5 p.m.	7 p.m.	8 a.m.	12 m.	5 p.m.	7 p.m.	
June 25	111	187	181	153	40	10	20	20	100 Gm. of carbohydrate
24	288	312	248	...	20	20	30	..	60 Gm. of protein
27	258	254	238	...	30	30	30	..	128 Gm. of fat
28	226	...	163	...	30	30	30	..	1,800 calories
29	214	...	100	...	30	30	30	..	
30	227	234	...	...	30	30	30	..	
July 1	217	...	...	...	30	30	30	..	
2	171	183	95	...	30	30	30	..	
3	200	...	...	...	20	20	20	..	Discharged from hospital
6	173	...	...	...	20	20	20	..	
					To take 3 doses of insulin daily, 20 units each, for 2 weeks, then 2 daily doses of 20 units each				

sugar on admission was 732 mg. per hundred cubic centimeters; there were heavy acetonemia and heavy lipemia, with extreme glycosuria and acetonuria. On that day, between 2 and 10 p. m., he received hourly intravenous doses of insulin of 20 units each. Chart 3 shows the resultant uniform uninterrupted fall of blood sugar during this period, from 732 to 131 mg. per hundred cubic centimeters. The subsequent progress of this patient is shown in table 12.

INSULIN REACTIONS

Shortly after the discovery of insulin Banting and his co-workers described the reactions to insulin in rabbits, explaining these as being due to hypoglycemia, which develops several hours after the subcutaneous injection of insulin, and which can be eliminated by the injection of glucose.

In my work it soon became evident, however, that there is no definite relationship between the degree of hypoglycemia and the reaction, for large doses of insulin sometimes produce a reaction a long time after the

blood sugar has reached the value of 45 mg. per hundred cubic centimeters or less, and also in the presence of similar hypoglycemia there may be no reaction. Moreover, the injection of calcium will eliminate the reaction without increasing the blood sugar value.

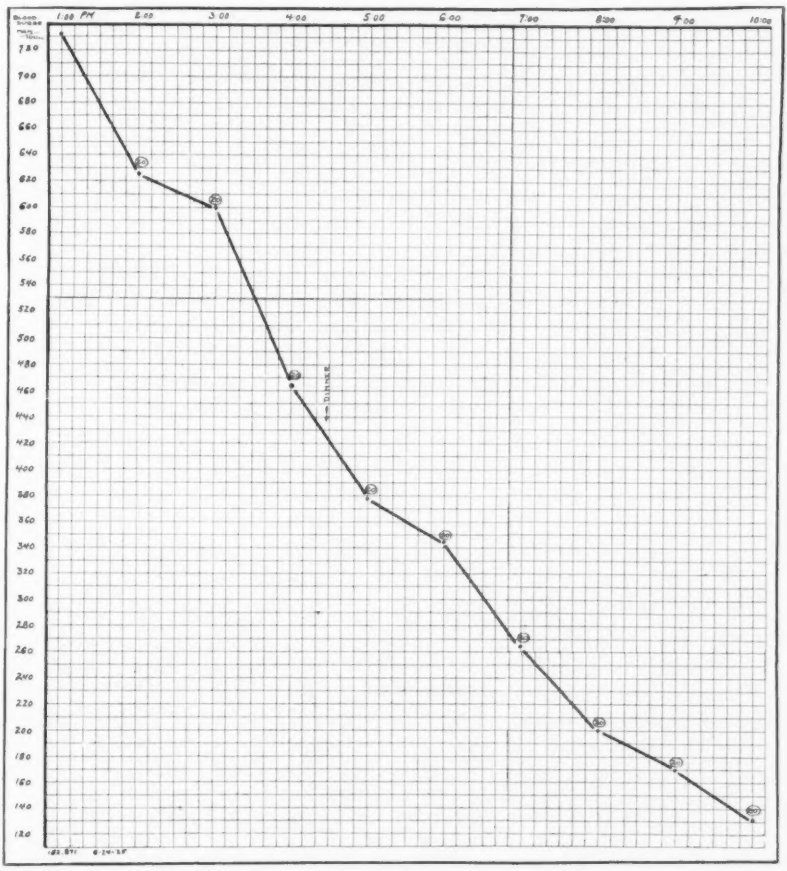

Chart 3.—The fall of blood sugar in a diabetic patient following hourly doses of insulin: the insulin dosage is indicated in the circles above the sugar curve.

It may be well at this point to describe the typical symptoms of an insulin reaction. The outstanding symptoms in the usual order of their occurrence are: (1) a feeling of anxiety; (2) pallor of the skin; (3) increased pulse rate and slight tremor of the hands; (4) a "sinking spell," the patient feeling weak and exhausted; (5) voracious hunger,

and (6) perspiration all over the body so profuse that the clothing may be drenched. Children will suddenly cry out even from a sound sleep as though terrified, and in children also a marked convergent nystagmus is often seen during a severe reaction. Any or all of these symptoms may appear. In my analysis of all cases in which a reaction occurred, which has included observations of the blood sugar before and at the time of reaction, and of the time interval between the administration of insulin and the reaction, I found that although in about 50 per cent

TABLE 13.—*Insulin Reactions: Relation of Blood Sugar Before and at Time of Reaction to Dosage of Insulin and the Length of Time Before Reaction Occurred (From Author's Study of One Thousand Cases of Diabetes)*

Blood Sugar Before Administration of Insulin, Mg. per 100 Cc.	Insulin Dosage, Units (Lilly)	Blood Sugar at Time of Reaction, Mg. per 100 Cc.	Time Between Administration of Insulin and Reaction, Minutes
400	20	186	60
102	30	51	45
286	56	246	8
93	42	59	30
153	10	55	60
256	31	67	90
197	20	62	60
167	20	57	95
196	20	125	5
222	12	110	20
40	15	40	Immediate
133	5	61	10
191	16	147	2
184	32	65	120
141	18	58	5
175	20	83	65
104	20	41	60
410	30	394	25
287	20	285	9
288	20	202	10
179	20	122	30

of the cases the reaction apparently was due to hypoglycemia, in nearly 50 per cent the reaction occurred when hyperglycemia was present. I found, moreover, that even in the same patient the reaction to insulin varied. Thus, a patient might have a low blood sugar content on one day and yet show no reaction even to large or repeated doses of insulin, while on another day when the blood sugar of the same patient was at a much higher elevation, a smaller dose of insulin would produce a marked reaction. In certain instances patients with such a marked hypoglycemia as 50 or 60 mg. per hundred cubic centimeters have shown no reaction after intravenous injection of from 20 to 40 units of insulin. In the case of one of my patients, a girl, aged 6 years, on one afternoon when the quantity of blood sugar was 38 mg. per hundred cubic centimeters (a fact that I did not know at the time) no reaction followed the intravenous injection of 20 units of insulin. It is obvious, therefore, that in many cases these reactions must be due to some other cause than hypoglycemia.

In the latest report from the Czech University at Prague, Mačela [2] states that they have succeeded in manufacturing insulin from which the substance that causes reactions has been chemically removed.

In table 13 I have summarized the reactions which have occurred in my own series with reference (1) to the height of the blood sugar

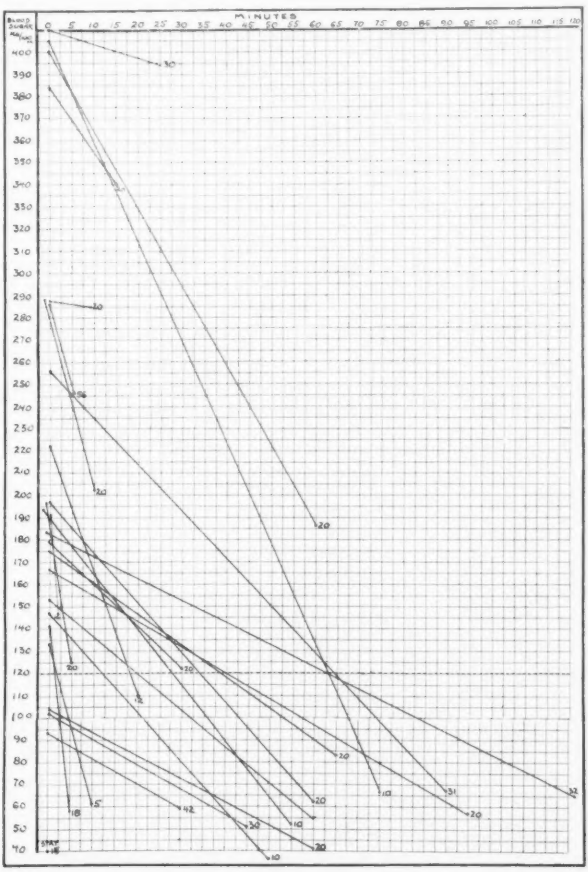

Chart 4.—The fall of blood sugar which accompanied reactions to insulin in twenty-four cases, and the length of time between the administration of insulin and the reaction.

before the insulin was given; (2) to the dosage of insulin given intravenously; (3) to the blood sugar at the time of the reaction, and (4) to the length of time between the administration of insulin and the reaction.

2. Mačela, I.: Čas. lék. česk. **64**:1515-1518 (Oct. 17) 1925.

Chart 4 gives the same data in a form that emphasizes the irregularity of these reactions. Thus, a reaction may occur immediately after the insulin has been given, or it may not appear until two hours or more later. The blood sugar content at the time of the reaction may be high, or it may be low. A reaction may follow a small dose of insulin in the presence of a marked hyperglycemia, and again no reaction may follow a large dose (10-40 units) of insulin in the presence of a low hypoglycemia. In other words, it is impossible to draw any general conclusions concerning these reactions as we do not know to what they are due. They certainly are not all due to hypoglycemia.

TABLE 14.—*Blood Examinations of Patients in Coma on Admission (From Author's Study of One Thousand Cases of Diabetes)*

Blood Sugar on Admission	Plasma Acetone	Plasma Carbon Dioxide	Outcome
200	+	40.4	Living
405	+	44.3	Living
434	+	19.2	Living
384	0	21.4	Living
353	+++	27.1	Living
400	++	21.4	Living
460	+++	38.5	Living
778	.....	21.4	Died
810	+++	9.9	Died
447	+	....	Died
652	+++	17.6	Died
300	.....	25.2	Died
267	+++	....	Died
333	0	....	Died

COMA

The total number of cases of coma included in this series is fourteen: seven of the patients are living and seven are dead. Of the seven living patients, two had relapses and were pulled through a second attack, one through a third attack. The seven patients who died were all in a critical condition when they arrived here, and died from one to a few hours after their admission to the hospital.

Fourteen other patients living outside of the city developed coma during the first year after their discharge from the hospital. In all these cases the immediate cause of the coma was an intercurrent infection (boils, an infected finger, tuberculosis) and absolute disregard of the prescribed diet. All these patients died.

The laboratory data on the fourteen cases of coma cited above are given in table 14. It will be noted that in this group of cases the blood sugar content ranged from 200 to 810 mg. per hundred cubic centimeters; the acetone in the blood plasma ranged from 0 to 3 plus, and the carbon dioxide combining power ranged from 44.3 to 9.9 mm., the higher figures being due to the administration of insulin previous to the examination, the results of which are here given.

As for the treatment of patients who are first seen in a state of coma, as long as there is sugar and acetone in the urine one can feel safe in administering an initial dose of from 40 to 60 units of insulin every two hours, or every hour if a heavy glycosuria persists. Liquids should be given by mouth, preferably in the form of dilute lemonade or orange ade, and in large quantities, from 2,000 to 4,000 cc.

Even after a patient has recovered from coma, the administration of insulin should be continued to the extent, perhaps, of three daily doses

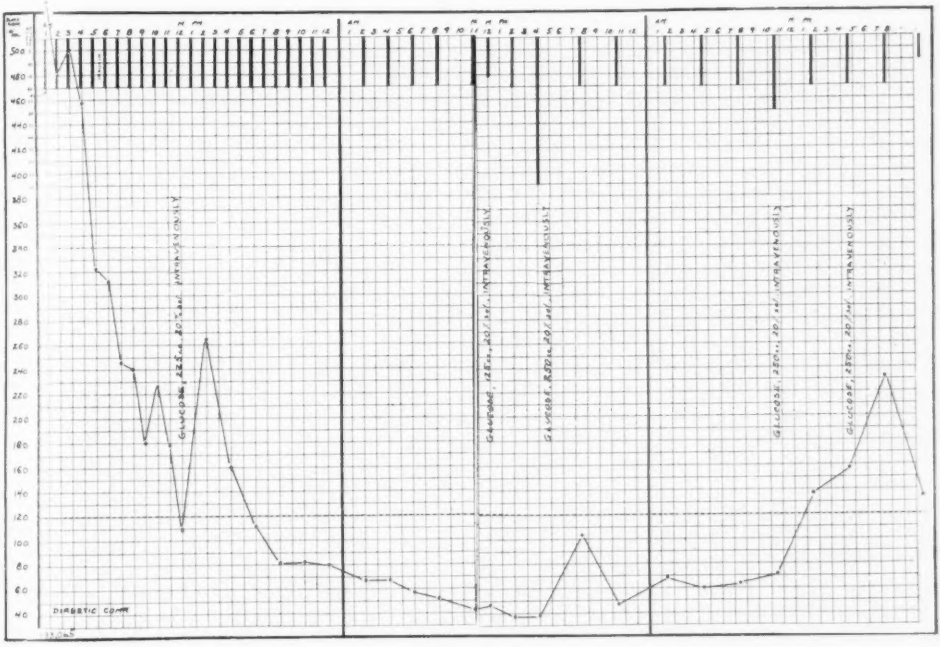

Chart 5.—The response of blood sugar to insulin and glucose in a patient in diabetic coma on three successive days.

of 20 units each unless reactions occur, in which case the dosage should be diminished accordingly. The diet is, of course, an important factor in the treatment. The intravenous injection of glucose supplies food and liquid which, with the aid of insulin, are properly metabolized, as is shown by the lack of its excretion in the urine. The injection of glucose is especially important in the case of an emaciated and weak person, as it serves to tide the patient over a crisis, but after two or three days the natural feeding by mouth must be relied on. Chart 5 shows the response to insulin and glucose on three successive days in the case of a patient in diabetic coma. Chart 6 shows the response in a case

of diabetes in which a cholecystenterostomy was performed. For seven days following the operation nothing was given by mouth, but all the nourishment was given intravenously in the form of a 10 per cent glucose solution in which insulin was incorporated. From this chart it can be clearly seen that glucose administered intravenously does not raise the blood sugar level even when continued over a longer period of time. Of course, it is true that no other form of nourishment had been given dur-

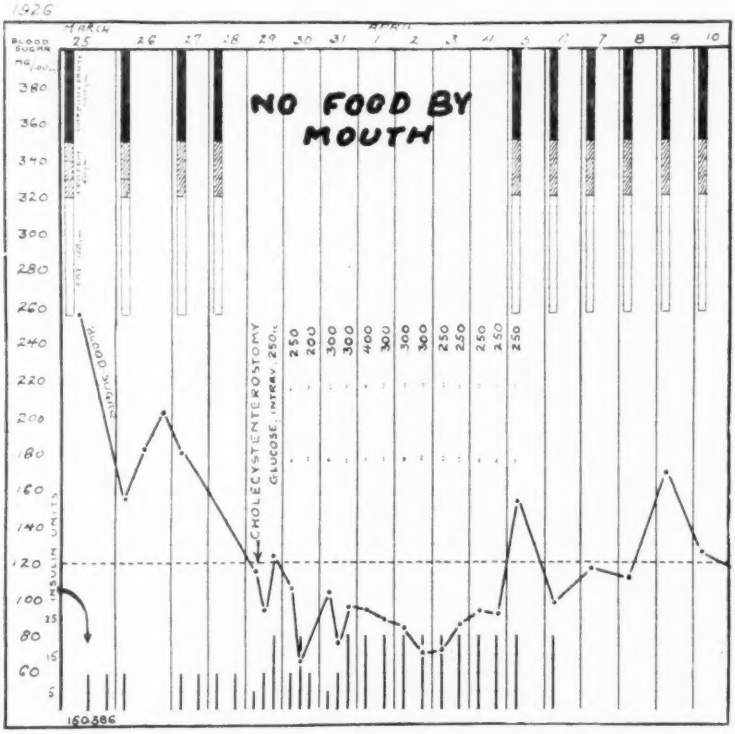

Chart 6.—The reaction to insulin in a patient before and after cholescystenterostomy.

ing this time, yet I feel that, in spite of this fact, this evidence tends to dispel the fear of administration of glucose solution intravenously. In the case of patients who are under treatment at home, repeated intravenous administration of glucose cannot be readily carried out, but a sufficient quantity of liquid can be supplied through a stomach tube after the stomach has been washed out.

The severity of the coma in any person may be judged by the degree of stupor; the characteristic forced Kussmaul type of breathing; the

markedly dry mouth and tongue; the flush of the cheeks; the exhaustion of the patient, which is manifested by a subnormal temperature; the failing circulation, which is manifested by the low blood pressure; and the vomiting of green or even hemorrhagic material, which often is profuse. These conditions constitute a terrific drain on the body, and one should try to reestablish the normal status as soon as possible in order to save the dwindling reserves. It should be emphasized that in giving insulin it is better to give too large a dose than one that is insufficient. Up to the present time I have not seen a reaction to insulin in any patient who has been under treatment for diabetic coma, the danger of a reaction practically being eliminated by the intravenous infusion of glucose.

In spite of large intravenous doses of insulin and glucose, and the application of all the other measures at our command, patients in coma die. One can say almost without reservation that they die because treatment is started too late. In coma, in which we are dealing with marked acidosis and with ketone bodies circulating in the blood stream, the heart bears the brunt of the extra load. Moreover, under any circumstances, the heart muscle of a diabetic patient has not the capacity of normal muscle for the storage of glycogen. This means that in an emergency its diminished glycogen supply is soon exhausted. The utilization of glucose even in the presence of a high blood sugar content is well illustrated by table 15. Moreover, the ketone bodies injure the heart muscle further, these two factors being, in part at least, responsible for the low blood pressure. Thus, the overstrained heart muscle, without reserves, and poisoned with the ketone bodies, is likely to give out at any moment. I saw a patient in coma die instantly as the result of an acute dilatation of the heart when she began to struggle in an attempt to get up, although the acidosis was beginning to be under control. The utmost physical rest is therefore extremely important.

Other conditions in which coma occurs which must be differentiated from diabetic coma are septicemia, meningitis, cerebral hemorrhage, uremia, traumatic concussion, morphine poisoning, encephalitis and insulin reaction. The differential diagnosis of diabetic coma from coma due to any of these conditions depends on the blood sugar. A marked hyperglycemia with or without marked glycosuria is found only in diabetic coma while the other conditions enumerated in the foregoing present only a slight rise of the blood sugar, or none at all. In uremic coma the blood urea is high, and it is thus a wise procedure in all cases of coma to estimate the blood urea in addition to the blood sugar, the acetone and the carbon dioxide. Moreover, even in a case of undoubted diabetic coma these examinations are of value as they throw light on the functional activity of the kidneys, and thus aid in indicating the prognosis.

INCIDENCE OF SYPHILIS IN DIABETES

Syphilis is a complication that is infrequently associated with diabetes. It is occasionally encountered, however, for a patient with diabetes is not immune to other infections. In this series of my own cases syphilis has been present in 2.6 per cent. A search of the literature shows that the majority of observers place the incidence of syphilitic infection

TABLE 15.—*Blood Sugar Changes Following Intravenous Administration of Glucose (From Author's Study of One Thousand Cases of Diabetes)*

Case	Blood Sugar Content and Time	10 per Cent Dextrose, Cc.	Blood Sugar Readings and Time
1	810 (3:35 p.m.)	250	706 (4:00 p.m.)
	612 (3:00 p.m.)	250	606 (4:15 p.m.)
2	123 (8:30 a.m.)	250	114 (11:30 a.m.)
	158 (9:00 a.m.)	250	182 (2:00 p.m.)
3	210 (10:30 a.m.)	250	187 (3:45 p.m.)
	216 (10:25 a.m.)	500	194 (3:20 p.m.)
	204 (3:30 p.m.)	500	191 (5:00 p.m.)
4	277 (10:00 a.m.)	500	238 (12:10 p.m.)
5	554 (11:00 a.m.)	250	323 (7:30 p.m.)
	300 (9:00 a.m.)	125	145 (5:00 p.m.)
6	109 (12:00 m.)	250	263 (2:00 p.m.); 160 (4:00 p.m.); 111 (6:00 p.m.)
	46 (12:00 m.)	125	87 (2:00 p.m.); 38 (4:20 p.m.)
	38 (4:30 p.m.)	250	103 (7:30 p.m.)
	71 (10:30 a.m.)	250	137 (1:30 p.m.); 157 (4:30 p.m.)
7	467 (3:51 p.m.)	250	410 (5:50 p.m.)
	423 (10:18 a.m.)	2 0	497 (11:30 a.m.); 348 (12:37 p.m.)
	348 (12:37 p.m.)	250	330 (1:30 p.m.); 300 (2:30 p.m.); 316 (3:30 p.m.)
	316 (3:30 p.m.)	250	309 (4:30 p.m.); 250 (5:30 p.m.); 282 (6:30 p.m.)
	344 (9:00 a.m.)	250	380 (11:00 a.m.); 348 (1:00 p.m.); 294 (3:00 p.m.)
	294 (3:00 p.m.)	250	300 (5:00 p.m.); 248 (7:00 p.m.)
	563 (12:00 m.)	250	497 (2:00 p.m.); 475 (4:00 p.m.)
	475 (4:00 p.m.)	250	410 (6:20 p.m.)
	475 (11:00 a.m.)	250	370 (1:00 p.m.); 243 (3:00 p.m.); 116 (5:00 p.m.)
	116 (5:00 p.m.)	250	50 (7:00 p.m.)
	389 (11:00 a.m.)	250	300 (1:00 p.m.); 272 (5:00 p.m.)
	428 (11:00 a.m.)	250	336 (2:00 p.m.); 258 (5:00 p.m.)
	258 (5:00 p.m.)	250	208 (7:00 p.m.)
	309 (11:30 a.m.)	2 0	240 (2:00 p.m.); 171 (3:30 p.m.)
	171 (3:30 p.m.)	250	171 (5:00 p.m.); 134 (7:01 p.m.)
	410 (11:00 a.m.)	250	375 (2:00 p.m.); 252 (5:35 p.m.)
	735 (8:30 a.m.)	250	416 (11:00 a.m.)
8	256 (9:25 a.m.)	250	316 (11:00 a.m.)
	316 (11:00 a.m.)	250	352 (1:00 p.m.)
	352 (1:00 p.m.)	2 0	120 (7:25 p.m.)
	416 (11:30 a.m.)	250	344 (2:00 p.m.); 114 (4:35 p.m.)
	114 (4:35 p.m.)	250	53 (7:00 p.m.)
	172 (10:35 a.m.)	250	176 (12:30 p.m.); 85 (2:30 p.m.); 63 (4:30 p.m.); 67 (6:30 p.m.)

associated with diabetes between 2 and 3 per cent. Joslin [3] found 1.7 per cent in a series of 3,200 cases. Rosenbloom,[4] on the other hand, found syphilis to be present in 11 per cent of a series of 139 cases (table 16).

Warthin and Wilson [5] state that within the last nine years in the necropsy service of the pathologic laboratory at the University of Michigan there have been six necropsies in cases of diabetes mellitus all

3. Joslin (footnote 1) pp. 586, 605.

4. Rosenbloom, J., cited by Joslin (footnote 1, p. 611).

5. Warthin, A. S., and Wilson, U. F.: Am. J. M. Sc. **152**:157-164 (Aug.) 1916.

of which showed histologic changes characteristic of syphilis, and that in four of these spirochetes were demonstrated in the myocardium and in one in the pancreatic lesions also.

DIABETIC SURGERY

A number of years ago Foster [6] looked up the mortality statistics of operations on diabetic patients in several hospitals, and on averaging them, found that in 45 per cent infection developed, this high figure demonstrating a lowered resistance. According to him, these patients also have a low recuperative power and the tissue repair is sluggish, these being the principal factors responsible for the high mortality rate. Joslin [7] has pointed out the high incidence of diabetes among obese persons. A fat diabetic patient, on the other hand, as pointed out by Foster,[6] indicates a mild stage of the disease, which, however, will become severe in time if the patient is untreated. If an obese diabetic

TABLE 16.—*Incidence of Syphilis in Diabetes (Compiled from the Literature)*

Author	Number of Cases of Diabetes	Number of Cases of Syphilis	Incidence, per Cent
Joslin (The Treatment of Diabetes Mellitus, pp. 586, 605)	3,200	55	1.7
John	1,000	26	2.6
Williams (cited by Joslin, p. 605)	143	4	2.7
Rosenbloom (cited by Joslin, footnote 1, p. 611)	139	16	11.0
Smith (Virginia M. Month. **49**: 662, 1923)	79	2	2.5
Fitz and Murphy (cited by Joslin, p. 140)	50	5	10.0
Von Saun (Joslin, p. 606)	12	1	1.3
Hirschfeld (cited by Rosenbloom: J. A. M. A. **68**: 1232, 1917)	.....	..	6.0

patient starts vomiting after an operation, he is in greater danger of acidosis than a patient who is underweight, and he will thus require the intravenous administration of glucose and insulin in order to combat the acidosis.

Infection in a diabetic patient diminishes the ability of the patient to utilize carbohydrates, and therefore the blood sugar content increases; this in turn causes an incomplete combustion of fat, with the appearance of ketone bodies in the blood and in the urine, and acidosis develops early and quickly. Increase of temperature also causes an increased metabolism, which in turn contributes to the production of acidosis. If present, nausea and vomiting automatically limit the fluid intake, a condition which in itself alone aggravates the acidosis and is likely to precipitate coma, owing to the fact that since the intake of food is inadequate the body tissues are drawn on for the increased demands of protein for energy. In consequence, there is increased protein catabolism, which is evidenced by the elevated urinary nitrogen, and the fat

6. Foster, N. B.: Surgical Aspects of Diabetes, J. A. M. A. **84**:572-576 (Feb. 21) 1925.

7. Joslin (footnote 1) p. 140.

catabolism is increased, especially in obese persons. It is for this reason that the intravenous administration of glucose together with insulin in cases in which there is vomiting is an efficient medical measure.

The effects of anesthesia in a diabetic patient do not differ in kind from the effects in other patients, but they are more pronounced. Ether anesthesia increases the blood sugar. In one of my cases, that of a boy, aged 5 years, a tonsillectomy was performed under ether anesthesia which lasted for fifteen minutes. The blood sugar before the administration of the anesthetic was 303 mg. per hundred cubic centimeters; immediately after the operation it was 434 mg. per hundred cubic centimeters; but there was no change in the carbon dioxide content of the blood nor in the plasma acetone. In one of my diabetic cases, after the removal of a cyst from the breast under ether anesthesia the blood sugar rose from 122 to 303 mg. per hundred cubic centimeters, the plasma acetone to 2 plus, the plasma carbon dioxide to 42.4 per cent by volume, and there were marked clinical signs of acidosis.

Dewes [8] ascribes the slight increase in the glycemia which occurs during local anesthesia for extraperitoneal operations entirely to the anesthetic. The increase in the glycemia is much greater in laparotomies than in other operations, sometimes amounting to from two to four times the normal figure.

Pemberton and Cunningham [9] also report that ether anesthesia in a diabetic patient produces a more severe hyperglycemia and a greater fall in the alkali reserve than in a nondiabetic patient, but that this can be controlled by the use of insulin. In spite of the use of insulin, however, the postoperative sepsis appears to produce both hyperglycemia and a low alkali reserve, although the latter complication can be corrected by alkali therapy.

Seitz [10] studied the blood sugar in cases of exophthalmic goiter and found a high hyperglycemia, which he thinks is probably due to the increased irritation of the sympathetic system. He found that fourteen days after operation the sugar metabolism and the tonus of the involuntary nervous system had become normal. He made the remarkable observation that after strumectomy in some cases of diffuse colloid goiter, the alimentary hyperglycemia and the sympathetic tonus were increased.

Tables 17 and 18 show the general mortality in my series of 1,000 cases of diabetes to be 6.2 per cent, with an operative mortality of 20 per cent. Four of the patients who died, however, should properly be excluded from this list. In case 3, in which erysipelas developed,

8. Dewes, H.: Arch. f. klin. Chir. **122**:173-187, 1922.

9. Pemberton, H. S., and Cunningham, L.: Lancet **2**:647-648 (Sept. 27) 1924.

10. Seitz, E.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **34**:514-526, 1922.

death occurred from this cause. In case 4, only an exploratory operation was performed; a general carcinomatosis being discovered, no further operation was performed, and the patient died a few months later. In case 6, in which a leg was amputated, gangrene developed in the other leg, the patient dying from the infection without surgical intervention. In case 7 death was not the result of the operation but of the extreme severity of the diabetes, the patient being markedly emaciated and

TABLE 17.—*Operative Mortality in Diabetic Patients (From Author's Study of One Thousand Cases of Diabetes)*

Total number of diabetic cases	1,000
Died (various causes)	62
Mortality, per cent	6.2
Diabetic patients operated on	35
Operative mortality	7
Mortality, per cent	20
Corrected mortality, per cent	8.5

Type of Operation	Age	Cause of Death
Thyroidectomy	67	Myocardial failure
Thyroidectomy	43	Myocardial failure
Mastoid*	48	Erysipelas
Cancer of liver* (exploratory operation)	78	General carcinomatosis
Thyroidectomy	72	Cardiac failure
Amputation of leg*	61	Gangrene of other leg
Abscess of lung*	58	Emaciation and exhaustion

* Excluded from "corrected mortality" for reasons stated in text.

TABLE 18.—*Operations Performed on Diabetic Patients in the Cleveland Clinic Hospital (From Author's Study of One Thousand Cases of Diabetes)*

Operations	Number of Cases	Died
Thyroidectomy	12	4
Amputation of leg	10	1
Resection of rib	2	1
Prostatectomy	2	..
Cholecystectomy	1	..
Resection of breast for tumor	1	..
Laparotomy	2	1 (general carcinomatosis)
Tonsillectomy	3	..
Resection of cecum for carcinoma	1	..
Mastoidectomy	1	..

exhausted. If, then, these four cases are excluded, the operative mortality becomes 8.5 per cent. It will be further noted from the table that the remaining deaths were all in cases of hyperthyroidism, which seems to be especially hazardous in the presence of diabetes. It appears that with the use of compound solution of iodine (Lugol's solution) this danger will be eliminated. Joslin [11] reports that in the fourteen operations by F. H. Lahey on Joslin's diabetic patients for disease of the thyroid gland there was but one death.

A general summary of operative mortality in diabetic cases as reported in the literature is given in table 19.

11. Joslin (footnote 1) p. 629.

PREOPERATIVE AND POSTOPERATIVE TREATMENT OF PATIENTS WITH DIABETES

After an operation on a diabetic patient the first forty-eight hours is the crucial period which determines the outcome. During that period it is essential that the internist direct the treatment, and that he be thoroughly informed regarding the progress of the patient, not daily but hourly. The anticipation and prevention of postoperative complications is the essential feature of successful postoperative treatment.

It is of especial importance that vomiting be prevented. By the use of nitrous oxide oxygen anesthesia or local anesthesia this is almost eliminated. If orange juice and coffee with sugar is given to the patient

TABLE 19.—*Operative Mortality in Diabetic Cases (Compiled from the Literature)*

Author	Year	Number of Operations	Mortality, per Cent
Morrison (Boston M. & S. J. **175**: 54, 1916)	1896-1913	775	23
Karewski (Deutsche med. Wchnschr. **40**: 8, 1914)	1914	68	11.8
Berkman (Journal-Lancet **36**: 309, 1916)	1915	26	7.6
Strouse (M. Clin. Chicago **2**: 37, 1916)	1916	38	31
Joslin (The Treatment of Diabetes Mellitus, p. 426)	Before 1917	27	18
	1919	61	9
Fitz (M. Clin. N. Amer. **3**: 1107, 1920)	1918	45	30
Mugind, H.	1921	5	80
Weeden (J. A. M. A. **82**: 1165, 1924)	1897-1922	160	36.8
		12	16.6*
Binney	1916-1923	32	19
Jones (Boston M. & S. J. **188**: 483, 1923)	1923	8	25
Young (Boston M. & S. J. **188**: 767, 1923)	1918-1922	99	16.1
Adams and Wilder (Wisconsin M. J. **22**: 557, 1924)	1924	327	1.2
Lahey	....	14	7.1†
Foster N. B. (J. A. M. A. **84**: 572, 1925)	1925	..	45‡
John	1921-1925	35	20
Corrected mortality			8.5

* Insulin cases.
† Thyroid.
‡ Statistical report from several hospitals.

early on the morning of the operation, it will help to prevent acidosis, with the resultant nausea and vomiting. It is also a good routine procedure to give the patient, as soon as he is off the operating table, an intravenous infusion of 250 cc. of 10 per cent glucose solution to which has been added 10 units of insulin. It is important that this solution should be made with freshly distilled water to prevent reactions. This infusion is an excellent preventive measure against acidosis, it supplies both food and liquid to the body, and the insulin helps to burn up the carbohydrate and incidentally the acid bodies which may be present in the blood. With a good start thus induced, the further progress of the patient will usually take care of itself. The glucose can be repeated if indications for it exist. It is a good plan when giving glucose to precede the injection by the withdrawal of about 8 cc. of blood for examination for sugar, acetone and carbon dioxide, as the information thus secured gives definite information as to the patient's status. I always administer insulin intravenously so that at the time each dose is given I can secure

a specimen of blood through the same puncture, and can thus follow every phase in the progress of the case from day to day, or more frequently if necessary. One cannot have too many data on a case, for too few data may be misleading. It does no harm to withdraw from 2 to 5 cc. of blood daily, or several times a day for the first three or four days.

The postoperative course of patients treated according to the routine outlined in the foregoing has been uneventful. However, no measure is of avail if a patient has a septicemia from gangrene or from an infected gallbladder. Thus, a blood culture will be of great help in judging the prognosis in any given case.

It is important that the patient should receive abundant liquids. If for any reason they cannot be taken by mouth or by rectum, hypodermoclysis should be instituted immediately and kept up until the patient is able to take sufficient fluid by mouth.

The use of insulin has also been of great aid in the control of other than diabetic operative cases. I believe it is a good routine measure to use it in small doses in any operative case as long as the patient is in the hospital, whether or not it is indicated by the blood sugar estimations. It should be borne in mind that certain cases are functional cases of diabetes. This, however, cannot always be determined with certainty, as it often takes weeks or months to establish the status. In cases of functional diabetes there is a good chance that the islands of Langerhans may be restored, provided a properly balanced diet is given; but the restoration may be hastened by the addition of insulin. Insulin is of little, if any, value in the anatomic type of diabetes in which fibrosis of the islands of Langerhans is present, but it also can do no harm in such cases. Thus, as long as we do not know with which type of case we may be dealing, or whether or not any given case may be a potential case of diabetes—since in many operative cases the pancreas must share in the general debility of all the organs and tissues—we can play safe by using insulin.

To illustrate a typical record in an operative diabetic case, I offer one of many similar records in chart 7.

A man, aged 62, in childhood had had measles and mumps; later, rheumatism and erysipelas. He came to the Cleveland Clinic, June 7, 1924, because his toe was turning black. On May 30, he had noticed a slight abrasion on his toe. He had applied iodine but the toe began to swell, and in forty-eight hours it began to become discolored. The man did not know that he had diabetes, as he had apparently been in perfect health up to that time; he had lost only 10 pounds (4.5 Kg.) in weight, and had not been a heavy eater. When he came to the clinic, his blood sugar content was 222 mg. per hundred cubic centimeters, and glycosuria was present; the Wassermann reaction was negative. He was placed in the diabetic hospital of the Cleveland Clinic on routine diabetic treatment, and ten days later, as the gangrene was beginning to spread, the right leg was amputated below the knee. In thirty-two days he

was discharged from the hospital. The stump had completely healed, the blood sugar content was normal, and it was not considered necessary for him to take insulin. Subsequent blood sugar examinations gave a normal result even after his diet was increased.

This patient apparently had a mild case of diabetes with a senile type of arteriosclerosis, which had as much to do with the production of the gangrenous condition as did the diabetes.

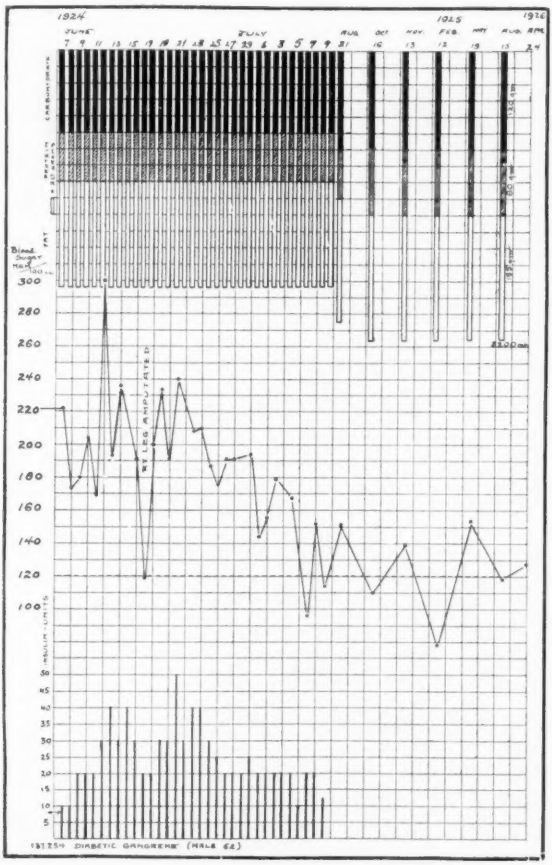

Chart 7.—A typical chart illustrating the progress of a diabetic patient after operation.

DISCOVERY OF DIABETES DURING EXAMINATION FOR LIFE INSURANCE

That in many cases the first indication of a diabetic condition is disclosed by an examination for life insurance is generally recognized. In 3.9 per cent of this series the condition was thus discovered, and this

is a lower percentage than is given in Joslin's [12] review of the literature on this point (table 20). Examinations for life insurance are thus of considerable value in this connection, for most of the patients in whom diabetes was thus discovered would not have sought medical aid at that time. The condition would have been discovered eventually, but not until the general physical condition had been weakened and the pancreatic function more seriously injured, the gravity of the prognosis being proportionately increased.

SUMMARY

The incidence of diabetes among all diseases seen at the Cleveland Clinic during the period covered by this report on a series of 1,000 cases has been 1.8 per cent.

The percentages of males and of females in the series are practically equal.

TABLE 20.—*Increasing Frequency of Discovery of Diabetes During Examinations for Life Insurance*

Period	Number of Cases	Sex		Discovered by Life Insurance		
		Male	Female	Total, per Cent	Male, per Cent	Female, per Cent
After Joslin, 1893-1916.....	1,000	594	406	6	10	0
1916-1920.....	1,000	578	422	9	15	1
1920-1923.....	1,000	524	476	13	22	2
Author's series, 1921-1925....	1,000	466	534	3.9	2.9	1

The largest incidence of diabetes as shown by this series is in the sixth and seventh age decades.

The incidence of syphilis in this series was 2.6 per cent.

There was an hereditary history of diabetes in 4.6 per cent of these cases, a familial history in 5.1 per cent.

Diabetes was found through an examination for life insurance in 3.9 per cent of the cases.

The highest blood sugar level on admission was 908 mg. per hundred cubic centimeters in the case of a middle-aged man who has recovered sufficiently to carry on his occupation. Blood sugar figures as high as 310 mg. per hundred cubic centimeters were encountered without glycosuria. The diabetic renal threshold was high in many cases.

The general belief that insulin once used must always be continued is shown to be fallacious by the tabulation of cases in which good progress has followed the discontinuance of insulin.

The mortality rate in thirty-five operations on diabetic patients in this series was 20 per cent. By the exclusion of four cases in which

12. Joslin (footnote 1) p. 122.

death was due to septicemia, which was present at the time of the operation, or to inoperable carcinoma, the mortality rate is reduced to 8.5 per cent.

Insulin reactions were not due to hypoglycemia in nearly 50 per cent of my cases; in fact, actual hyperglycemia was demonstrated. In the comment on the time relation of the insulin reaction to the dosage of insulin and to the blood sugar level it has been shown that there is marked irregularity in the factors that are supposed to play a part in the production of this reaction.

In the twenty-eight cases of diabetic coma discussed, fourteen patients were under observation at the Cleveland Clinic. Among these fourteen, seven survived and seven died, the latter being brought to the hospital in extremis and dying in from one to a few hours after admission. In the other fourteen cases, the patients had been discharged from my service and were living outside the city when coma developed as the result of some intercurrent infection; all these fourteen patients died.

The blood sugar in the cases of coma at the clinic ranged from 200 to 810 mg. per hundred cubic centimeters; the plasma acetone from 0 to 3 plus, and the plasma carbon dioxide from 44.3 to 9.9 mm. of pressure. The higher figures in the last instance were due to the administration of insulin previous to the carbon dioxide determination.

DIET DETERMINATIONS

A GRAPHIC METHOD *

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A graphic method of determining the protein, fat and carbohydrate constituents of a diet, without calculation, is presented in this article. The method is adapted for use with diets of any caloric content up to 5,000 calories and for a range of fat-carbohydrate ratios from 1:2 up to 4:1. A chart of this type, that is equally serviceable for a large variety of dietary requirements, has not, so far as we are aware, appeared in the previous literature.

The triangular diagram of the type used by Du Bois [1] is of equally general application; this gives protein, fat and carbohydrate in percentages, however, and correlates them with the respiratory quotient; it is therefore less convenient for use when total caloric intake and fat-carbohydrate ratio are two of the arbitrarily fixed constants in the determinations.

For the determination of diets in diabetes, two nomographic charts have been published, that of Hannon and McCann,[2] and that of Wilder.[3] The former, which is an ordinary Cartesian diagram, is based on the Woodyatt [4] FA/G ratio, in which its value is 1.5, and diets can be determined by it for this value of the ratio only. The elements of the Woodyatt FA/G ratio, as is well known, are calculated from the following formulas: $G = C + 0.58\ P + 0.1\ F$, and $FA = 0.46\ P + 0.9\ F$. With this, and the formula for total calories ($M = 4.1\ C + 4.1\ P + 9.3\ F$), the Hannon and McCann type of chart can be constructed.

Wilder's chart is an alinement diagram, also limited to a single fat-carbohydrate ratio. It is based on a simplification of the Woodyatt formula. Wilder assumed that in 100 Gm. of protein there were 58 Gm. of carbohydrate, 16 Gm. of nitrogen and 26 Gm. of material

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* From the Department of Medicine, Columbia University, College of Physicians and Surgeons, and the Presbyterian Hospital, New York City.

1. Du Bois, E. F.: Basal Metabolism in Health and Disease, Philadelphia, Lea and Febiger, 1924.

2. Hannon, R. R., and McCann, W. S.: Bull. Johns Hopkins Hosp. **33**:128 (April) 1922.

3. Wilder, R. M.: Optimal Food Mixtures for Diabetic Patients, J. A. M. A. **78**:1878 (June 17) 1922.

4. Woodyatt, R. T.: Objects and Method of Diet Adjustment in Diabetes, Arch. Int. Med. **28**:125 (Aug.) 1921.

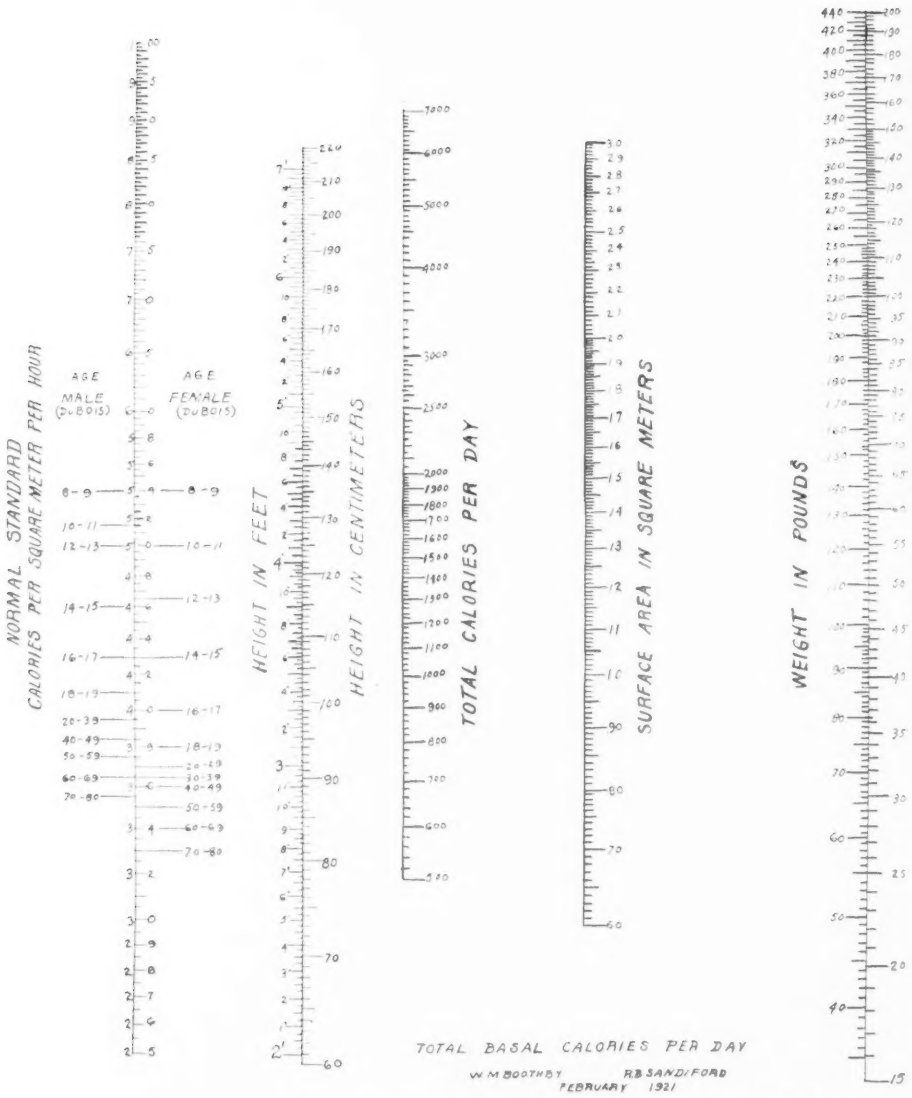

Chart 1.—Boothby and Sandiford's chart for the determination of basal food calory requirements.

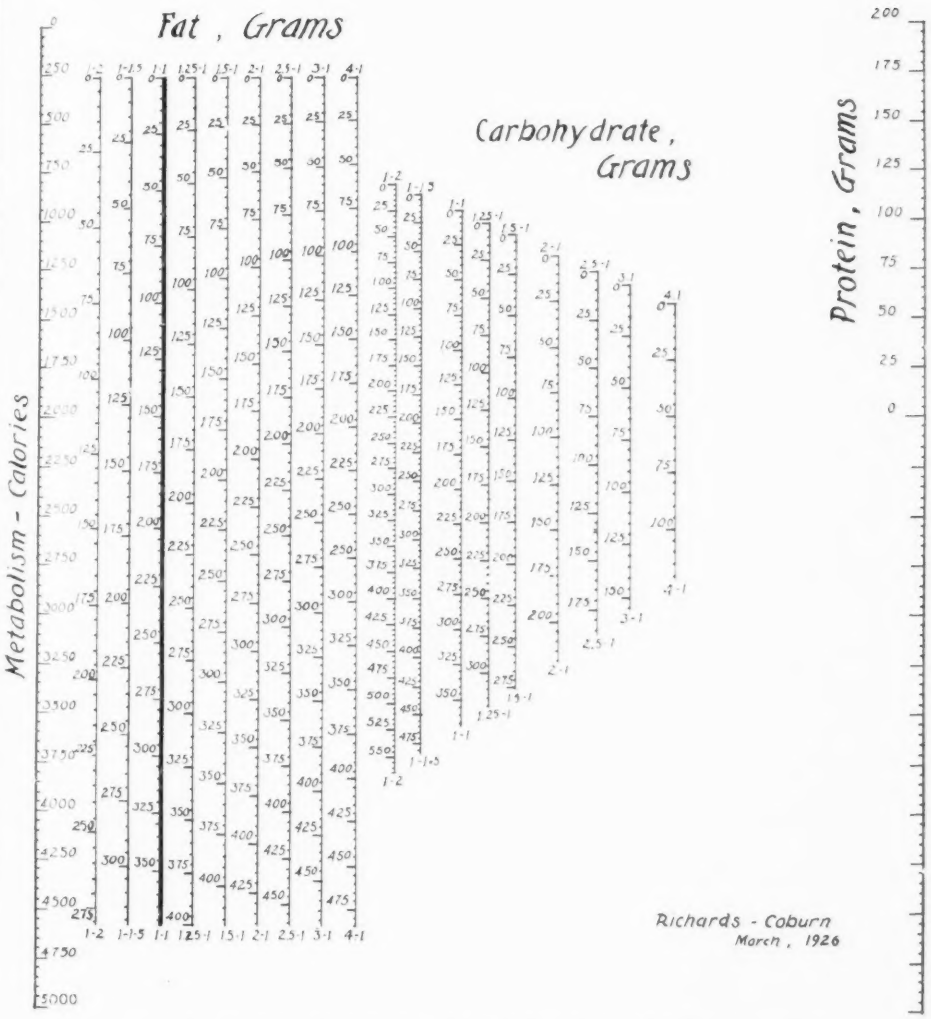

Chart 2.—Chart for determination of fat, carbohydrate and protein constituents of diets: (*a*) first scale, total calories; (*b*) next eight scales, grams of fat for eight different fat-carbohydrate ratios; (*c*) next eight scales, grams of carbohydrate for eight different fat-carbohydrate ratios; (*d*) last scale (right side of chart), grams of protein.

"either ketolytic or neutral." Calculating them all as ketolytic, in the form of aceto-acetic acid, he found that 23 Gm. of glucose would be needed for their combustion. By disregarding the glycerol fraction of the fat, Wilder's FA/G ratio then simplified to: $\frac{FA}{G}$ $\frac{F}{C + (0.58 - 0.23)\,P}$. To this FA/G ratio, Wilder assigned the value of 4.

For our FA/G or R values we have used the simple relationship $R = \frac{F}{C + 0.58\,P}$, as used by Palmer and Ladd[5] in their work on ketogenesis in diabetic patients. This has not all the theoretical accuracy of the Woodyatt or Shaffer[6] formulas, but is probably well within the general accuracy of calculation of diets by ordinary quantitative methods. This formula gives, of course, appreciable differences in R values, as compared with those given by the other formulas, but for most diets these differences will not be more than 0.2 or 0.3. Maximum differences would occur when P is large and C small, and F either very large or very small. If $F = 50$, for example, $C = 50$, $P = 100$, then R by the Wilder formula would be $\frac{1}{1.7}$; and by the Palmer-Ladd ratio which we have used, $R = \frac{1}{2.2}$.

CONSTRUCTION

The chart is a D'Ocagne nomogram, constructed in the same manner as Wilder's chart. The method has been described by Wilder, Henderson[7] and others in recent literature and will not be reviewed here. The basic formulas used are:

1. Ratio (Palmer-Ladd) $= \frac{\text{Gm. } F}{\text{Gm. } C + 0.58 \times \text{Gm. } P}$ in which available carbohydrate = (Gm. carbohydrate) + (0.58 Gm. protein), and fat = 100 per cent F.

2. Total calories = (9.3 × Gm. F) + (4.1 × Gm. C) + (4.1 × Gm. P).

Because of the mechanics of construction, values for carbohydrate requirements fall on discrete parallel vertical lines for each fat-carbohydrate ratio, and values for fat requirements fall on one vertical line for all ratios. As this difficulty defeats the purpose of the chart, an expedient is taken. The values of fat requirements for each ratio are transposed horizontally (from the points where they fall) to a parallel line drawn in at an arbitrary distance.

The average error in determining a diet by the use of this chart is not more than 2 Gm. of any constituent and less than 20 calories of the total calory scale. The accuracy is well within that obtainable by ordinary quantitative measurements of food substances.

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5. Ladd, W. S., and Palmer, W. W.: Proc. Soc. Exper. Biol. & Med. **18**:109, 1920; Am. J. M. Sc. **166**:157 (Aug.) 1923.

6. Shaffer, P. A.: J. Biol. Chem. **54**:399 (Oct.) 1922.

7. Henderson, L. J.: J. Biol. Chem. **59**:379 (March) 1924.

As will be seen, the chart can be used for almost all types of diet, as the fat-carbohydrate ratios range in value from 1:2 up to 4:1.

The complete system presented consists, as did that of Wilder, of two charts, the well known Boothby-Sandiford[8] chart for basal metabolic rate determinations (reprinted here by permission of the authors), and the one discussed above.

From the former (knowing weight, height, age and sex), twenty-four hour caloric requirements are determined as follows:

1. Locate weight and height points on their respective lines.
2. Connect these with straight edge, thus determining surface area.
3. Locate point on "normal standard" line.
4. Connect "normal standard" and surface area points with straight edge.
5. Straight edge then crosses calory scale at basal twenty-four hours' requirement.

To use the diet chart, the caloric requirement (basal, or basal + 50 per cent, etc.) must be known, and one of the food elements must be arbitrarily fixed. This will ordinarily be the protein value; for example, 1 Gm. per kilogram of body weight. A definite fat-carbohydrate ratio (*R*) must also be chosen.

With these values known, the fat and carbohydrate requirements are then read off as follows:

1. Locate protein and caloric requirements on their respective lines.
2. Connect these with straight edge.
3. The carbohydrate requirement can then be read on the proper *R* line.
4. The fat requirement can be read on heavy line for 1:1 ratio.
5. For any other ratio, the fat requirement is determined by observing the point where the straight edge crosses the 1:1 (heavy line), and then with this point as a center rotating the straight edge to the horizontal position and reading on the proper *R* line the fat requirement. (It will be noted that the protein line has been extended downward and graduated similarly to the calory scale in order that the straight edge may be fixed at the horizontal without difficulty.)

This chart is also of service in determining changes of diet, 'isodynamic shifts," etc.

SUMMARY

For the determination of the protein, carbohydrate and fat constituents of a diet, without calculation, a graphic method is here presented. This can be used for many types of diet, and for a wide range of fat-carbohydrate ratios.

8. Boothby, W. M., and Sandiford, R. B.: Boston M. & S. J. **185**:337 (Sept. 22) 1921.

FRAGILITAS OSSIUM AND DEAFNESS

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We report here four cases of blue sclerotics, brittle bones and deafness; three illustrate the symptoms and signs of the disease and one the familial transmission. The cases are characterized by blue sclerotics, early and continued occurrence of fracture, because of the fragile type of the bones, and sometimes the development in early youth of progressive deafness.

The disease is hereditary and a patient may have one, two or all symptoms. Children afflicted with the blue sclerotics alone usually die in infancy. When the blue sclerotics are first manifest in adolescence they are associated with brittle bones, and later deafness may supervene.

HISTORY

Stobie,[1] in reviewing the literature, noted only twenty-seven cases or family groups: twenty-four from England and Germany and three from this country. Conlon[2] reported six cases in one family from Boston, Ostheimer[3] one case in a child of Russian Jew parentage from Philadelphia, and Herrman[4] one case from New York. We have been able to find reports of seven other families and cases in the American literature; most of these cases occurred east of the Alleghenies. Wise[5] presents a group of six cases from Baltimore, Van der Veer and Dickinson[6] two cases from Albany, Mixsell[7] one case from New York

1. Stobie, William: The Association of Blue Sclerotics with Brittle Bones and Progressive Deafness, Quart. J. Med. **17**:274-287 (April) 1924.

2. Conlon, F. A.: Five Generations of Blue Sclerotics and Associated Osteoporosis, Boston M. & S. J. **169**:16-19, 1913.

3. Ostheimer, Maurice: Fragilitas Ossium, J. A. M. A. **63**:1996-1999 (Dec. 5) 1914.

4. Herrman, Charles: Blue Sclerotics Associated with Brittle Bones; Report of a Case in a Child Two Years Old, Am. J. Dis. Child. **9**:205-212, 1915.

5. Wise, W. D.: Fragilitas Ossium with Blue Sclerotics, J. A. M. A. **73**:1696 (Nov. 29) 1919.

6. Vander Veer, E. A., and Dickinson, A. M.: Fragilitas Ossium, Ann. Surg. **74**:629-632 (Nov.) 1921.

7. Mixsell, H. R.: Osteogenesis Imperfecta (Osteopathyrosis, Fragilitas Ossium), with Report of Two Cases, Arch. Pediat. **34**:756-764 (Oct.) 1917.

City, Goldbloom [8] one from Montreal, Rodriguez [9] one from Fort Wayne, Ind., Terry [10] two from San Francisco, and Flagstad, Zanger and Leven [11] two typical cases from St. Paul. Two cases were observed in the Mayo Clinic in 1924, and three cases in 1925; the patients were from Wisconsin, Illinois and Missouri.

REPORT OF CASES

CASE 1.—A man, aged 20, came to the clinic, Sept. 6, 1924, complaining of pain in the back and the right hip. In June he had consulted a physician for palpitation of the heart. A blood test was said to be positive for syphilis and he was given an injection in the right gluteal region. Later two blood tests were negative. The injection caused severe pain for several days, then disappeared until August when it returned and interfered greatly with walking and

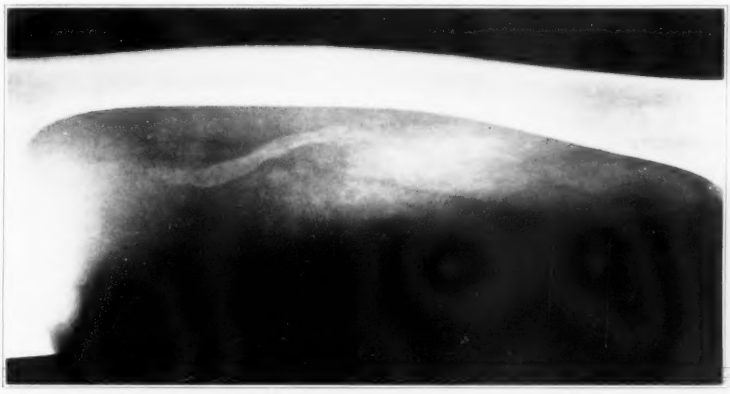

Fig. 1.—Myositis ossificans (case 1).

sleeping. There was a constant dull ache with sharper exacerbations when weight was placed on the right leg. Slight fever accompanied the pain.

At the age of 15 years the patient fractured an elbow by bumping it against a barn door. Later he fractured the other elbow by knocking it against the saddle while riding horseback. Two ribs were fractured by a kick of a horse. A rock fell on his leg and fractured the ankle. Two years later a fall from a wagon resulted in fracture of the collar-bone. He sprained his ankle on one occasion and his present trouble with his back appeared to be somewhat similar.

His mother said that his paternal grandfather, a German immigrant of Wisconsin, had had blue sclerotics. His father also had blue sclerotics, was deaf,

8. Goldbloom, Alton: Fragilitas Ossium, with Report of a Case, Canad. M. A. J. **7**:636-640 (July) 1917.

9. Rodriguez, J.: Idiopathic Osteopsathyrosis, J. Indiana State M. A. **17**:111-113 (April) 1924.

10. Terry, W. I.: Hereditary Osteopsathyrosis, Ann. Surg. **68**:231-234 (Aug.) 1918.

11. Flagstad, A. E.; Zanger, Elizabeth; and Leven, Logan: Blood Chemistry Study in Osteogenesis Imperfecta; Preliminary Report, Minnesota Med. **7**:800-804 (Dec.) 1924.

and in his youth had had a fracture of the leg which failed to unite; the leg was finally amputated. The patient is one of nine children, six boys and three girls. Five of the family have blue sclerotics; one sister has had both arms and one leg broken; the other two sisters are deaf, and one brother has had a leg broken. Except for one brother in South Dakota, the family is living in Wisconsin.

Fig. 2.—Anterior view (case 2).

The patient's sclerotics were deep blue. When he entered the clinic he had a temperature of 102 F., which subsided within a few days. The leukocyte count was normal. Roentgenograms revealed hypertrophic arthritis and lateral curvature with rotation of the lumbar spine, areas of myositis ossificans in the muscles of the right thigh (fig. 1), and ununited fractures of both elbows. It was believed that the pain in the back and hip was due to irritation of the nerve roots from rotation of the spine, and the patient was fitted with a short corset. The serum calcium was 8.5 mg., and the organic phosphorus 4.4 mg. for each hundred cubic centimeters of blood.

CASE 2.—A man, aged 47, came to the clinic, Oct. 27, 1924, complaining of a gradually increasing pain in the right hip of twenty years' duration. He was 4 feet, 5.5 inches tall and weighed 108 pounds (49 Kg.) (figs. 2 and 3). When the patient was 2 years old, he fell off the bed and fractured his right arm. The same year he refractured it by a fall. Eight years later a snowball struck his right arm and fractured it in a different place, and within a year it was refractured three times by a thrown ball and slight injuries. At the same time

Fig. 3.—Lateral view of patient showing posture (case 2).

he fell off a horse and struck his head. As a result he carried his head to the left and had it immobilized for six weeks. When he was 12 years old a post fell on his thigh and broke his right femur. The next year he fell out of a buggy and broke his right collar-bone. When fourteen he jumped from a cart and broke his left femur. At the age of 27 he fell from a wagon and refractured his left femur. The patient has not grown since he was 10 years old. He has had deformities of head and legs as long as he can remember, but he was never aware of his blue sclerotics. Sexual power was normal in youth but has dimin-

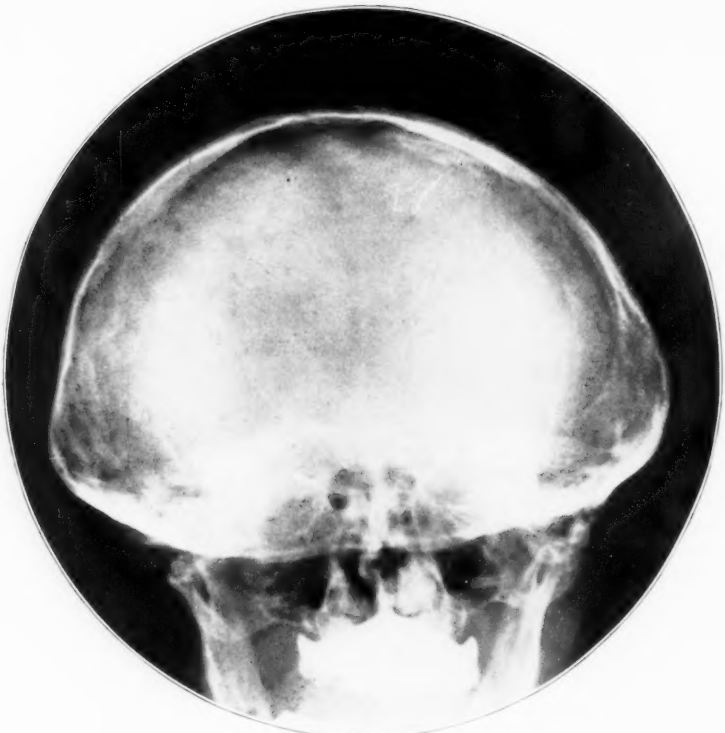

Fig. 4.—Head (case 2).

Fig. 5.—Head (case 2).

ished in the last twenty years. He has three brothers and four sisters, none of whom has blue sclerotics or brittle bones. Two brothers are deaf in one ear as a result of mastoidectomy.

The sclerotics were not as blue as in the first case; however, the color was distinctly deeper than normal. There was marked horizontal and vertical nystagmus, probably congenital. Roentgenograms (figs. 4 and 5) revealed marked

Fig. 6.—Bowing of bones of leg and sclerosis of posterior tibial artery (case 2).

bony deformity of the head, deformity of the pelvis with destructive arthritis of the right hip joint which accounted for the pain, bilateral rudimentary cervical ribs, slight arthritis of the hands, destruction of the body of the tenth dorsal vertebra, an old fracture of the lower third of the right humerus, and marked bowing of the tibiae and fibulae (fig. 6). Certain of the long bones showed considerable atrophy. There was slight glycosuria with a fasting blood sugar of 110 mg. for each hundred cubic centimeters. The serum calcium was 8.1 mg., and

the inorganic phosphorus was 4.6 mg. for each hundred cubic centimeters of blood. Hearing was normal. Arteriosclerosis grade 3 was found.

Case 3.—A woman, aged 49, came to the clinic, Feb. 29, 1925, complaining of nausea and vomiting, pain in the joints and severe headaches. The patient was the smallest of her family and had been aware of the blue sclerotics all her life. Deafness had been gradually increasing since her twentieth year. She said that her mother had been partially deaf in old age and that a sister was somewhat deaf. No one of her immediate family was especially susceptible to fractures. She had two nephews and a grandniece with blue sclerotics and the grandniece

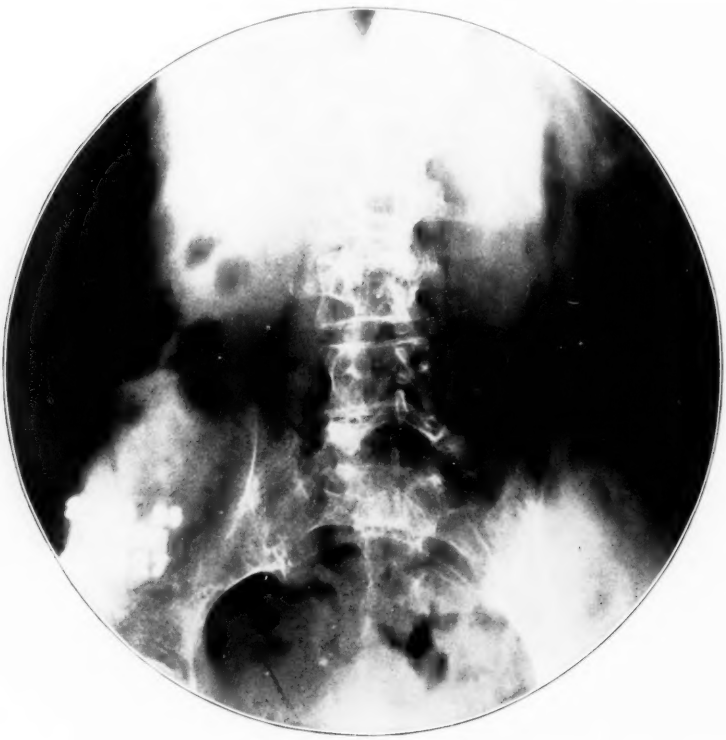

Fig. 7.—Pelvis (case 3).

also had brittle bones. A questionnaire sent to all branches of the patient's family gave the information that there were no blue sclerotics, brittle bones or deafness in the grandparents, parents, brothers or sisters or their children.

The patient was only 4 feet, 9 inches tall and weighed 70 pounds (31.8 Kg.). She had marked generalized arteriosclerosis. The systolic blood pressure was 192 and the diastolic 118. The blood urea was 72 mg. for each hundred cubic centimeters, and the phenolsuphonphthalein return was 30 per cent. The sclerotics were grayish blue with darker zones corresponding to the ciliary bodies, and there was a wide arcus senilis. The fundi showed moderate retinal arteriosclerosis of the hypertension type. There was advanced deafness of the nerve on both sides. Roentgenograms (fig. 7) revealed considerable porosity of the bones of the extremities and marked atrophy of the bones of the spine and pelvis.

CASE 4.—A woman, aged 52, came to the clinic because of a severe pain in her back. She also noticed that she was becoming shorter in stature. She presented the syndrome of blue sclerotics, brittle bones and progressive deafness. Her family history was traced through several generations and it was seen that she was a member of the third generation in which this syndrome had appeared. At present the members of the family are living in two states, Illinois and Oklahoma, but the ancestor in whom it first appeared lived in Waterford County, Ireland. The Irish grandmother had had blue sclerotics and suffered from frequent fractures, but was never deaf. Despite her disabilities she lived to the ripe old age of 95. She gave birth to three sons, one of whom inherited the blue sclerotics. One of the other two sons died at the age of 35; the other still living, has seven children, none of whom has blue sclerotics. The son with blue sclerotics was the father of eleven children, of whom the patient and five others inherited this characteristic. His oldest daughter has two children, one with, the other without it. The patient has five children, three with and two without the syndrome. The third child, a boy with blue sclerotics, is living and unmarried; the fourth son has two children, a boy with and a girl without blue sclerotics. The other two children with blue sclerotics died in infancy (fig. 8).

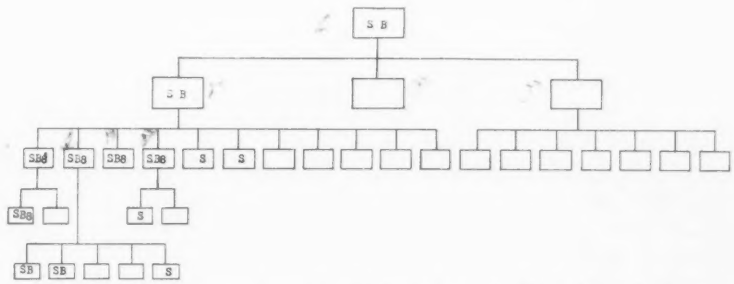

Fig. 8.—Family diagram (case 4): *S*, blue sclerotics; *B*, brittle bones; 8, nerve deafness; squares containing *S* alone indicate infants or those dying in infancy who had blue sclerotics but did not have time to develop indications of brittle bones by fractures.

COMMENT

In all reported cases the color of the sclerotics was uniform. No matter in which direction the eyeball was turned the homogeneous leaden blue was seen through the scleral conjunctiva. The color was so distinct as to leave no doubt as to its significance. It is variously described as a porcelain or leaden blue, and appears to be due to an increased transparency of the sclerotics allowing the choroid to shine through, rather than to an extraordinary thinness. Bronson [12] has quoted six cases of the syndrome from the literature and added a seventh in which no hereditary tendencies were demonstrable. She notes that the sclerotics were not so blue in her patient as in the group from the literature.

The fractures may be spontaneous or associated with trauma. Roentgenograms have revealed atrophy of the bone. Patients are also said

12. Bronson, E.: On Fragilitas Ossium and Its Association with Blue Sclerotics and Otosclerosis, Edinburg M. J. **18**:240-281 (April) 1917.

to be susceptible to sprains. In case 2 the changes in the shape of the head with the flattening in both directions and the overhanging parietal bosses seems to be characteristic of the fragilitas ossium group. The relation of the deformity of the sella region, caused by the changes in the head, to the existing infantilism and glycosuria is an interesting subject for speculation. The type of infantilism apparent in this case resembles more closely that commonly called essential infantilism than the type that is the result of rickets, fragilitas ossium and similar bony changes, although manifestations of the latter type may also be included. The relation of the syndrome of blue sclerotics and brittle bones to the conditions known as fragilitas ossium, osteogenesis imperfecta and osteopsathyrosis is unknown. It is noteworthy that many authors of case reports of these diseases make no mention of color in the sclerotics nor of hereditary tendencies. For this reason some cases of blue sclerotics are probably included in these other groups. The accompanying deafness seems to be due to otosclerosis, a lesion of the auditory nerve.

The most plausible explanation for the cases of blue sclerotics with brittle bones and deafness is that they are caused by a congenital mesenchymal defect, since all the structures involved in the syndrome come originally from this anlage. However, this theory does not explain why other tissues of mesenchymal origin, such as the heart, blood and lymph vessels, bone marrow and lympth nodes, are not usually affected.

The third case is of unusual interest because of the associated cardiovascular degeneration. This degeneration, of course, may be coincidental but it also may be logically explained on the basis of an original defect in the mesenchyme. Very few cases of this syndrome have been reported in which there was involvement of the cardiovascular system. The atrophy of the bone was so great that had the patient led a more active life it is likely she would have had multiple fractures. The discrepancy between the patient's account of trouble similar to hers in other members of her family and the actual facts brought out by the questionnaires and the relatives shows that great care must be exercised in working out the family history in this type of case. Other associated defects, such as kyphosis, congenital heart disease, spina bifida and cleft palate, also occur.

Little is known of the metabolism of inorganic salts in these cases. Like Flagstad, Zanger and Leven, we have found normal values for serum calcium and inorganic phosphorus.

Case 4 is illustrative of the hereditary tendency of the syndrome. In this tree, all who lived beyond seventeen years had begun then, if at all, to show deafness, and the factor of brittle bones manifested itself in early childhood and throughout life in multiple fractures. It is interesting to note that approximately 50 per cent of the children of

each heir with blue sclerotics inherited the syndrome in whole or in part and in turn transmitted it. The other 50 per cent did not inherit and did not, in any part of their chain, manifest nor transmit a tendency to this syndrome. No definite sex linkage in transmissions nor immediate sequence was noticed in this particular family. The meaning of immediate sequence may best be illustrated by example; that is, if we could foretell that a person with blue sclerotics would have four children, from our investigations we could not say how the 50 per cent tendency would follow, whether the first and fourth child, the second and third or the second and fourth in order of birth would have blue sclerotics and other manifestations of this syndrome. Neither does the presence of the syndrome seem to have any direct bearing on the longevity of the individual, for three members of this family have lived well over seventy-five years, the grandmother to 95.

In summing up the hereditary tendencies of this syndrome and its apparent 50 per cent transmission, we shall use the formula Guyer [13] sets forth in his book "Being Well-Born." He says, "In man as in lower forms some characters or traits are due presumably to the presence of determiners or their absence." He uses what he calls a "presence-absence" formula with the symbol *A* for the determiner and *a* for its absence. Thus *AA* represents a condition in which similar determiners have been derived from both parents and which is called duplex; *Aa*, a condition in which the determiner is from only one parent and hence simplex, and finally *aa*, in which there is total absence of determiner and which is called nulliplex. From these pairs, six kinds of combinations are possible:

1. *aa* x *aa*	*a-a*	All nulliplex
	x	
	a-a	
2. *aa* x *Aa*	*a-A*	50 per cent nulliplex
	x	
	a-a	50 per cent simplex
3. *aa* x *AA*	*a-A*	All simplex
	x	
	a-A	
4. *Aa* x *Aa*	*A-A*	25 per cent duplex
	x	50 per cent simplex
	a-a	25 per cent nulliplex
5. *Aa* x *AA*	*A-A*	50 per cent duplex
	x	
	a-A	50 per cent simplex
6. *AA* x *AA*	*A-A*	All duplex
	x	
	A-A	

13. Guyer, M. F.: Being Well-Born, Indianapolis, Bobbs-Merrill Company, 1916.

In our case 4 we believe that the blue sclerotic is a simple dominant in the simplex form, and when united with a nulliplex as in formula 2, will produce offspring 50 per cent of whom show blue sclerotics. These, in their turn, will have an equal chance of transmitting blue sclerotics to 50 per cent of the next generation, and so on.

SUMMARY

In four cases with blue sclerotics, brittle bones and deafness presented, two are definitely hereditary while the other two reveal no familial tendency. The source of these groups seems to be from Europe. One of our cases definitely follows the mendelian law. The disease is uncommon. It is progressive although concomitant with longevity.

THE MECHANISM OF PAIN IN GASTRIC AND IN DUODENAL ULCER

III. THE RÔLE OF PERISTALSIS AND SPASM

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CHICAGO

It has been shown that hydrochloric acid is an irritant that constitutes an adequate stimulus to the pain-producing mechanism of a sensitive ulcer. In this article data are reported regarding, first, the rôle of peristalsis and spasm in the distress so produced, and, second, the effect of peritalsis as a mechanical stimulus to the pain-producing mechanism. This evidence gives some information as to the relationship of the pain-producing mechanism to the ulcer.

LITERATURE

In 1916, Ginsberg, Tumpowsky and Hamburger [1] reported the first experiments showing a muscle tension factor in ulcer pain. The following year Carlson [2] published some excellent kymographic tracings showing intermittent ulcer pain synchronous with gastric contractions, and concluded also that the pain was due, not to the acidity per se, but to the muscle tension. Hardt,[3] on the basis of similar work, drew the same conclusion a year later. In 1919 Homans [4] took exception to this view and contended that powerful, vigorous contractions of the fundus of the stomach might be present without pain and pain present without any contractions of the fundus. In 1922 Reynolds and McClure,[5] on the basis of their roentgenologic studies, concluded that there was no incontrovertible evidence of the relationship of ulcer pain to motor activity. Ortmayer [6] in 1925 confirmed Homan's work, and concluded that the pain of ulcer is not related to muscle tension but to the acidity

1. Ginsberg, Harry; Tumpowsky, Isidor; and Hamburger, W. W.: Contributions to the Physiology of the Stomach: XXXV: The Newer Interpretation of Gastric Pain in Chronic Ulcer, J. A. M. A. **67**:990 (Sept. 30) 1916.

2. Carlson, A. J.: Contributions to the Physiology of the Stomach: The Origin of Epigastric Pains in Cases of Gastric and Duodenal Ulcer, Am. J. Physiol. **45**:81 (Dec.) 1917.

3. Hardt, L. L. J.: Pain in Active Pathologic Processes in Stomach or Duodenum, J. A. M. A. **70**:837 (March 23) 1918.

4. Homans, John: The Relation of Pain in Gastric and Duodenal Ulcer to Muscular Activity of the Stomach, Am. J. M. Sc. **157**:74 (Jan.) 1919.

5. Reynolds, L., and McClure, C. W.: Motor Phenomena Occurring in Normal Stomachs, in Presence of Peptic Ulcer and Its Pain, as Observed Fluoroscopically, Arch. Int. Med. **29**:1-11 (Jan.) 1922.

6. Ortmayer, Marie: Gastric Motor Activity in Patients with Peptic Ulcer, Arch. Int. Med. **35**:423 (April) 1925.

of the gastric content. In 1921, Poulton [7] reported that the distress of gastric ulcer could be initiated by increasing gastric tension, and relieved by its reduction. Hurst [8] ascribes the pain to muscle tension. Ryle [9] states that "given an irritative focus, the ingestion of food, or the readiness for it, even in the absence of acid secretion, is an adequate stimulus for the initiation of the exaggerated tonic and peristaltic action upon which the pain depends."

METHODS OF STUDY

Previous investigators of the mechanism of ulcer pain were all handicapped by their inability to initiate and relieve the pain at will. It was necessary to wait for spontaneous pain, which occurred at a time when the stomach contained food. The sole exception was in Carlson's case, his patient evidently having an extremely sensitive pain mechanism. The success of the acid injections altered the situation entirely and afforded a method for studying the stomach and duodenum before, during, and after the induction and relief of pain.

Two main lines of investigation were followed in this study. The first was the balloon method used by Carlson and others in the study of hunger contractions. In this the patient swallows a small rubber condom, about 5 inches (12.7 cm.) long, which is attached through a small rubber tube to a water manometer. A flag floats on the water manometer, and its up and down strokes are recorded on a revolving drum. It was customary to inflate the balloon system with 120 cc. of air. When the balloon was allowed to pass into the duodenum, a smaller quantity of air was used, usually 20 cc., occasionally 10 cc., or at times 30 cc. The balloon was usually tied to the side of a Rehfuss tube in order that material could be withdrawn from or injected into the stomach at will. When the balloon and one Rehfuss tube were in the duodenum, a second Rehfuss tube was usually kept in the stomach. The difficulties encountered are well known to other investigators. The patients soon learn to tolerate the apparatus with very little discomfort. One man repeatedly swallowed four rubber tubes at one time, two of them being of the Rehfuss type. In the intestinal work, it was found necessary to examine the patient fluoroscopically frequently in order to detect changes in the position of the balloon. This was usually done at the beginning and end of each tracing. With this method, it is possible to obtain a satisfactory record of the conditions present in the fundus and body of the stomach and in the second and third portions of the duodenum, but very little evidence is obtained as regards the

7. Poulton, E. P.: Lancet **1**:263 (Feb. 5) 1921.

8. Hurst, A. F.: The Sphincters of the Alimentary Canal, Brit. M. J. **1**:145 (Jan. 24) 1925.

9. Ryle, J. A.: Gastric Function in Health and Disease, London, Oxford Univ. Press, 1926, p. 961.

condition of the gastric antrum, the pylorus, and the duodenal cap. These are, of course, the usual sites of lesion. It is difficult, if not almost impossible, to get a balloon to remain constantly in one of these positions during periods of filling and emptying of the stomach. Hence, it was necessary to resort to the roentgenologic method of study.

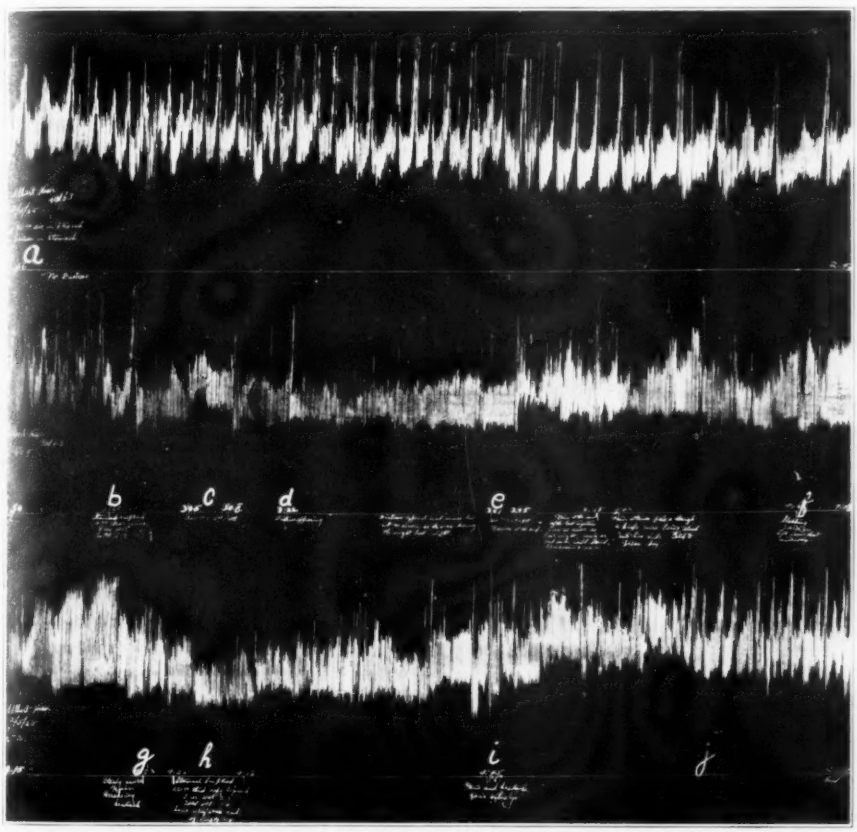


Fig. 1 (experiment 157).—Consecutive record of patient with active gastric ulcer with 120 cc. of air in 6¾ inch balloon in stomach: *a*, 1:36, beginning of period of type 1 hunger contractions without pain; *b*, 2:58, stomach emptied of 10 cc. of clear juice, free acidity 15, total 23; *c*, 3:05-3:08, 200 cc. of 0.5 per cent hydrochloric acid solution by Rehfuss tube; *d*, 3:22, distress appearing; *e*, 3:41-3:45, distress typical and severe; 200 cc. of 0.5 per cent hydrochloric acid solution; pain at once made nearly as severe as the patient can endure; *f*, 4:12, momentary stabbing pain; *g*, 4:23, steady severe pain continued, accompanied by headache; *h*, 4:25-4:28, stomach emptied of 130 cc. of thick ropy liquid, free acidity 23, total 34; some relief at once; *i*, 4:45, pain and headache gone entirely; *j*, 5:05, painless contractions reappear.

Reynolds and McClure [5] had made fluoroscopic observations of the stomach during pain, using meat mixed with barium and waiting for spontaneous distress to appear. Sippy [10] had made similar studies by giving barium at a time when spontaneous distress was present and making the observations before the distress disappeared. This suggested the second method used, that of giving barium made up in a 0.5 per cent solution of hydrochloric acid to patients with pain-producing mechanisms which were known to be sensitive, and observing the changes before, during and after the induction of pain, as well as after it had been relieved by an alkali. Satisfactory results were obtained. A preliminary fluoroscopic study was made of the effect of this acid barium solution on normal stomachs.

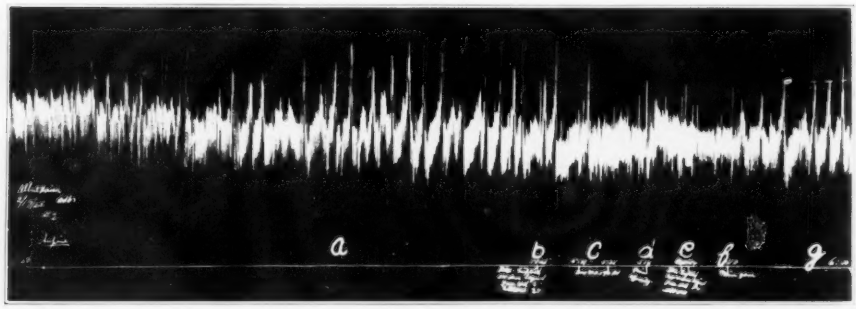


Fig. 2 (experiment 169).—Record of same patient as figure 1 with 120 cc. of air in 6¾ inch balloon in stomach: *a*, 5:10, painless type 1 hunger contractions; *b*, 5:26, stomach emptied of 5 cc. of clear liquid, free acidity 30, total 38; *c*, 5:31-5:35, 200 cc. 0.5 per cent hydrochloric acid solution given; *d*, 5:41, pain appeared; *e*, 5:50-5:54, stomach emptied of 200 cc. of clear liquid, free acidity 84, total 95; *f*, 6:10, pain entirely gone; *g*, 6:15, painless type 1 hunger contractions reappeared.

RESULTS OF THE BALLOON METHOD

The accompanying tracings are illustrative of the results obtained by the balloon method. The three in figure 1 represent a portion of one experiment in a patient with a sensitive gastric ulcer. The first tracing shows a period of good type 1 hunger contractions, without any distress. In the second tracing, the contractions stop (*b*) and distress appears (*d*) fourteen minutes after the injection of the acid (*c*). This distress becomes more and more severe without any pronounced increase in the intragastric tension until it becomes about as severe as the patient can stand. At times it is stabbing in character (*f*). The third tracing shows the disappearance of the pain (*i*) seventeen minutes after the emptying of the stomach (*h*) and the gradual reappearance of gastric motility without distress (*j*). The fourth tracing shows again in the same

10. Sippy, B. W.: Personal communication to the author.

patient on another day the manner in which the painless type 1 hunger contractions are stopped by the injection of the acid (*c*), pain produced (*d*) without any particular alteration in intragastric tension and without marked gastric motility, the distress relieved (*f*) by emptying the stomach (*e*), and the resumption of gastric motility without distress (*g*).

In figure 2 the same phenomena are shown again. The balloon was in the stomach of a patient with a sensitive duodenal ulcer. The very vigorous hunger contractions stop before the emptying of the stomach at *c*; acid is injected at *d*; intragastric tension decreases somewhat; pain appears at *f* with no motility and with less tone than was present just previously without pain, and pain disappears at *h* after emptying the stomach at *g*.

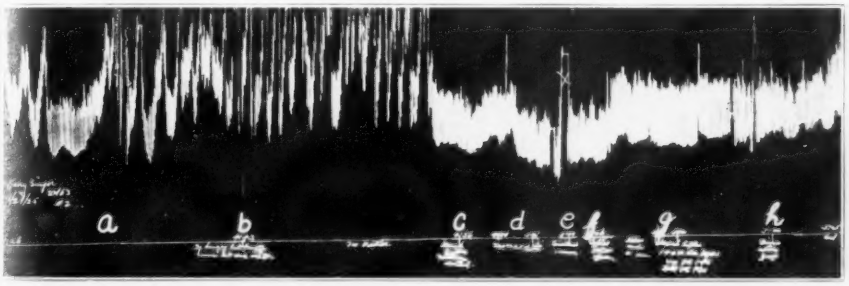


Fig. 3 (experiment 148).—Record of patient with active duodenal ulcer with 120 cc. of air in 6¾ inch balloon in stomach: *a*, 4:30, beginning of period of good type 1 hunger contractions; *b*, 4:43, hunger but no other distress; *c*, 4:56, stomach emptied, nothing obtained; *d*, 4:59-5:01, 200 cc. of 0.5 per cent hydrochloric acid solution given; *e*, 5:04, considerable nausea; *f*, 5:06, typical distress appeared; *g*, 5:11-5:12, distress remained the same; stomach emptied of 140 cc. of clear liquid, free acidity 140, total 146; *h*, 5:20, pain gone entirely.

The tracings in figure 3 are from an experiment in which the balloon was in the descending portion of the duodenum of a patient with an active duodenal ulcer. The good duodenal contractions (*a*) are painless and are not altered by the injection of warm water into the stomach (*b*). Following the injection of acid into the stomach (*e*), spasm of the duodenum occurs, but pain does not appear in this case until (*f*) after the cessation of the spasm. The pain continues without especial duodenal activity or noteworthy change in tone, and completely disappears at *m* twenty minutes after emptying the stomach at *j*. The tracings in figure 4 show the same phenomena in the descending portion of the duodenum in another patient with an active duodenal ulcer.

An entirely different type of thing is shown in the tracings of figure 5, taken with the balloon in the stomach of a patient with multiple gastric

ulcers and a highly sensitive pain-producing mechanism. In the first portion (*a*) of the first tracing, a mild continuous distress is present, not related to the gastric activity and relieved by emptying the stomach (*b*). In the remainder of this tracing, definite intermittent pains are

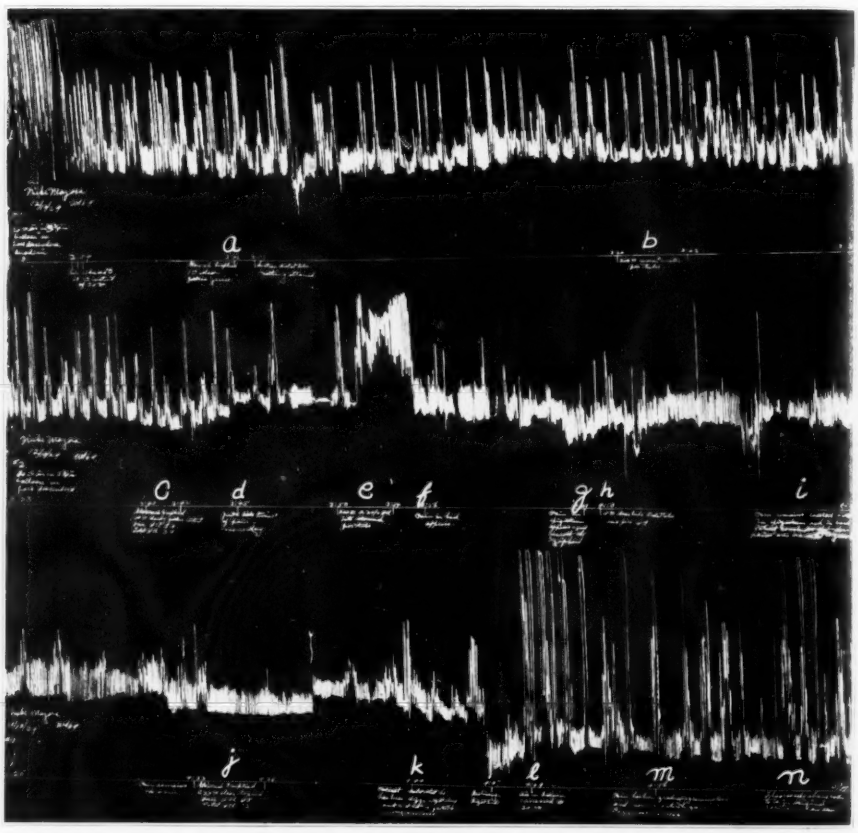


Fig. 4 (experiment 96).—Consecutive record of patient with active duodenal ulcer with 10 cc. of air in 3¼ inch balloon in pars descendens duodeni: *a*, 3:02, stomach emptied of 1 cc. of clear gastric juice; *b*, 3:20-3:23, continuous painless contractions unaffected by 200 cc. of warm water injected into the stomach; *c*, 3:40-3:42, stomach emptied of 100 cc. of cloudy gastric content, free acidity 34, total 39; *d*, 3:45, momentary twinge of pain; *e*, 3:50-3:54, 200 cc. of 0.3 per cent hydrocloric acid injected into stomach; *f*, 3:56, pain in back appeared after the spasm had disappeared; *g*, 4:09, pain in epigastrium appeared; *h*, 4:10, 5 cc. of clear bile in distal tube, no free hydrochloric acid; *i*, 4:20, pain remained severe both in epigastrium and back and patient concluded that "these pains are connected together;" *j*, 4:33-4:36, pain remained the same; stomach emptied of 230 cc. of clear liquid, free acidity 68, total 72; *k*, 4:44, patient stated that he was dizzy and that the dizziness was steadily increasing; *l*, air in balloon increased to 30 cc.; *m*, 4:56, pain entirely gone, dizziness less; *n*, 5:07, fluoroscopic examination showed balloon to be in its original position in pars descendens duodeni.

registered (*c*) synchronous with each of the gastric hunger contractions. Six days later, good hunger contractions are present in this patient without pain, as is shown in the second tracing (*a*). The ulcer is still very sensitive to acid, but the pain is not so severe as at the time of the preceding experiment. In this patient apparently a more sensitive pain-producing mechanism was required for the production of pain by means of the contractions than was required for its production by means of acid.

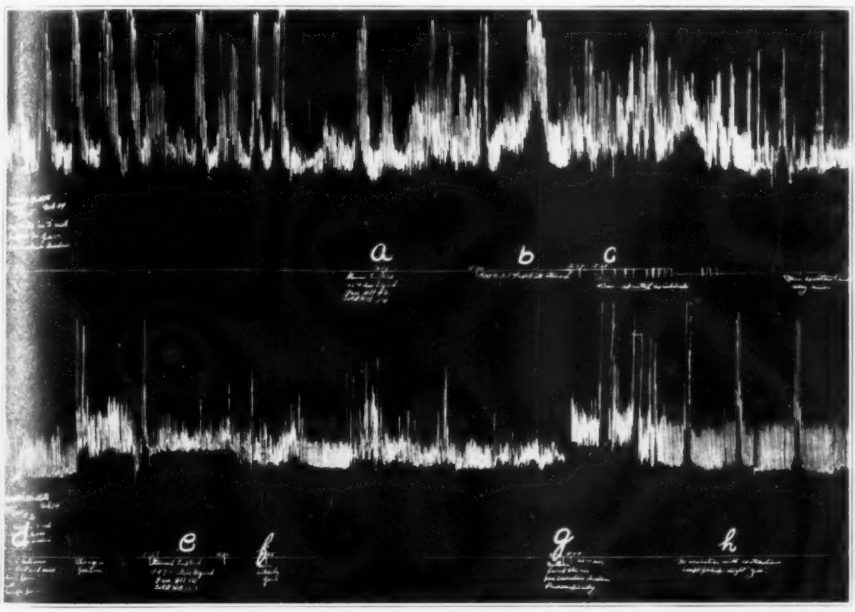


Fig. 5 (experiment 249).—Consecutive record of patient with active duodenal ulcer with 20 cc. of air in 3 inch balloon in pars descendens duodeni: *a*, 3:12, stomach emptied of 105 cc. of clear liquid, free acidity 42, total 54; *b*, 3:20, 400 cc. of 0.5 per cent hydrochloric acid solution injected into stomach; painless duodenal spasm; *c*, 3:29, remittent pain appeared, indicated by depressing the key of the signal magnet; *d*, 3:48, typical ulcer pain continued; *e*, 3:57-4:02, stomach emptied of 447 cc. of clear liquid, free acidity 121, total 127; *f*, 4:05, pain entirely gone; *g*, 4:30-4:44, balloon fluoroscopically found to be in pars descendens duodeni; *h*, painless contractions.

Figure 6 illustrates a third type of case. These records are all from a patient with a chronically perforated gastrojejunal ulcer, the base of which was formed by the anterior abdominal wall, and which was further complicated by a high grade inflammatory reaction in the surrounding tissue, as was evidenced by the large, tender palpable tumor mass. This mass disappeared gradually under treatment and the exact nature of

the lesion was proved at operation by Dr. Karl Meyer. In the first tracing, good type 1 hunger contractions are seen. These were productive of a "funny, grabbing sensation" (*b*) but no pain. One and a half hours later, 1.5 mg. of histamine hydrochloride was injected subcutaneously, and an hour later pain appeared. This pain was severe and was remitting in character, as is shown in the second tracing (*c*). The paroxysms of excruciating pain are seen definitely to accompany the

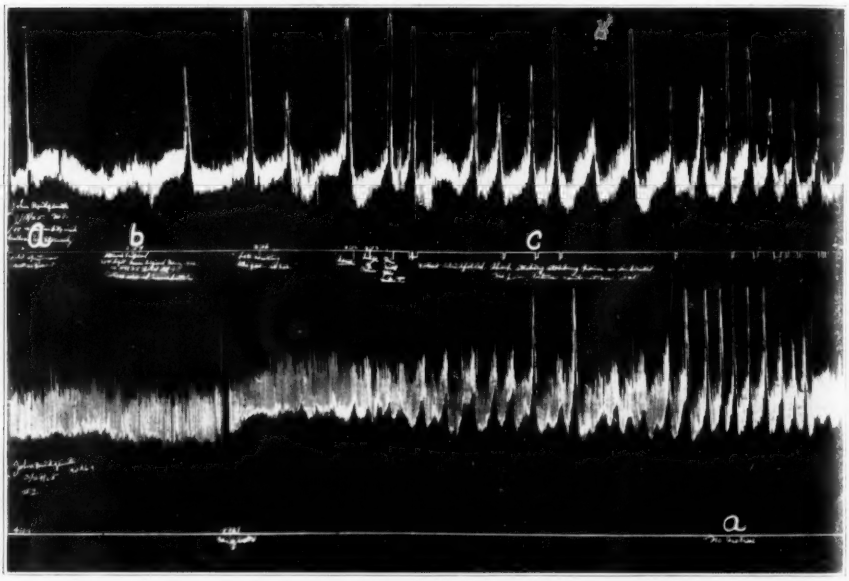


Fig. 6 (experiment 225).—Upper: Record of patient with multiple superficial highly sensitive gastric ulcers with 100 cc. of air in 6¾ inch balloon in stomach (patient blindfolded); *a*, 2:52, mild spontaneous distress present; *b*, 2:59, stomach emptied of 35 cc. of light brown liquid; benzidine test positive; free acidity 35, total 41; distress relieved immediately; *c*, pain with each contraction as registered, none between contractions. Lower: Record of same patient (experiment 221) six days later: *a*, painless contractions.

gastric contractions, but severe pain is also present between contractions, and pain continues for twelve minutes after the cessation of the contractions (*g* to *i*). Remitting pain with a definite peristaltic factor was frequently observed in this patient. The contractions registered in this tracing are much more powerful than in the preceding one. It was repeatedly observed that when pain was produced by allowing the extremely highly acid gastric secretion to accumulate or to remain unneutralized, the contractions would become more powerful. Acid seemed to sensitize the gastric motor mechanism as well as the sensory

mechanism. This is evident in the first two tracings. The third was taken an hour later, and it shows the reverse condition. Large doses of alkali had been given to neutralize the acid and relieve the pain. The gastric secretion was so excessive that the effect of the alkali was of brief duration. At 6:50 (*j*) the stomach was emptied of 95 cc. of liquid with a free acid of 93. Pain appeared at once (*k*) in spite of the emptying, severe, remitting in type, and accompanied by intense muscular activity. The pain was gradually relieved at *n* by heavy calcined magnesia and sodium bicarbonate (*l*, *m*), and at the same time the muscular activity became less intense. It might be reasoned that the decrease in the pain was due to the decrease in the muscular activity. This may be partly true. Certainly, the severest paroxysms of pain were synchronous with the most intense muscular activity. In the fourth tracing, however, made after ten days of antacid therapy, equally intense muscular activity is evident, but without pain. The gastric free acidity at this time was low, 23. This suggests that intense muscular activity is an adequate stimulus to the pain-producing mechanism only when this mechanism has been sensitized by hydrochloric acid. The definitely more intense muscular activity suggests that this acid sensitization may effect not only the sensory, but also the motor, mechanism.

It was seen in the tracings of figure 4 that a very sensitive mechanism may be stimulated by motor activity alone. However, six days later when the patient was having less severe spontaneous distress, peristaltic activity did not produce pain, but acid stimulation did. A higher degree of irritability was required, apparently, for the production of pain by means of peristaltic (mechanical) stimulation than was required for its production by means of chemical stimulation. Perhaps this higher degree of irritability was the result of acid sensitization.

It is possible that the pain-producing mechanism of an ulcer may be rendered so highly irritable by factors other than acid that the peristaltic stimulus alone is sufficient to effect pain. Proof of this can best be obtained by the study of the pain in ulcers with a true and complete achlorhydria. I have not had the privilege of observing such a case.

Table 1 shows the total relationship observed between pain and peristaltic activity, the different locations of the balloon being given. Pain without contractions was observed 198 times in all, whereas pain synchronous with the contractions was seen only nineteen times.

Table 2 represents a summary of the types of pain encountered in the study and the relative frequency with which a contraction factor was demonstrated in each. In 91.24 per cent of the pain no contraction factor was demonstrated.

EFFECT OF STARVATION AND INSULIN

The great majority of hunger contractions obtained were type 1. More powerful waves were seldom seen. The periods of starvation were usually from eighteen to twenty-four hours, but the possibility existed that if the starvation period were lengthened the waves might become more powerful and be productive of pain. It is a well-known clinical fact, however, that the pain of ulcer usually disappears on

TABLE 1.—*Relation of Pain to Contractions*

	Gastric	Duodenal	Total
Pain Without Contractions			
1. Constant Type			
(a) Stomach	88	62	150
(b) Pars descendens duodeni	12	18	30
(c) Pars inferior duodeni	1	3	4
2. Remittent Type			
(a) Stomach	2	4	6
(b) Pars descendens duodeni	1	1	2
3. Intermittent Type			
(a) Stomach	2	1	3
(b) Pars descendens duodeni	3	0	3
Total	109	89	198
Pain Synchronous with Contractions			
1. Constant Type			
(a) Stomach	0	0	0
(b) Pars descendens duodeni	0	0	0
2. Remittent Type			
(a) Stomach	15	0	15
(b) Pars descendens duodeni	2	0	2
3. Intermittent Type			
(a) Stomach	2	0	2
(b) Pars descendens duodeni	0	0	0
Total	19	0	19

TABLE 2.—*Summary of Relation of Pain to Contractions*

Type of Pain	Frequency of Occurrence, Percentage	Contractions		
		(a) The Only Factor, Percentage	(b) A Partial Factor, Percentage	(c) No Factor Demonstrated, Percentage
Constant	84.79	0	0	100
Remittent	11.52	0	65.22	34.78
Intermittent	3.69	25	—	75
Total relationship	.....	0.92	7.84	91.24

starvation. Nevertheless, experiments were carried out to decide this point. In some the blood sugar was further depleted by insulin, Bulato and Carlson [11] having shown that in normal animals insulin tends to increase gastric tone and motility.

Two patients with sensitive gastric ulcers were starved for four days without experiencing pain. One was then given 25 units of insulin, and the other 30 units. Insulin reactions resulted in both cases, but there was no pain and no marked increase in the strength of the hunger

11. Bulato, E., and Carlson, A. J.: Contributions to the Physiology of the Stomach: Influence of Experimental Changes in Blood Sugar Level on Gastric Hunger Contractions, Am. J. Physiol. **69**:107 (June) 1924.

contractions. Both were highly sensitive to acid at the end of the period. Three patients with duodenal ulcers were starved for three days each without the development of ulcer pain or unusually powerful hunger contractions. All remained very sensitive to acid. A fourth patient with duodenal ulcer was starved for three days without noteworthy increase in the intensity of his hunger contractions. This patient did have ulcer pain at times during the period of starvation, but it was shown to be related to an unusually large amount of fasting gastric secretion with a high free acidity, and not to peristaltic activity.

EFFECT OF ATROPINIZATION AND INTRAVENOUS GLUCOSE

Attempts were made to render the pain-producing mechanism unresponsive by means of atropinization, but without success. Neither could it be affected by intravenous injections of glucose, although Bulato and Carlson [11] have shown that intravenous injections of dextrose tend to inhibit gastric tone and motility in normal animals. These methods combined were also ineffective, as is illustrated in the following protocol:

EXPERIMENT 422.—*Prepyloric ulcer with obstruction; tincture of belladonna, 10 minims four times a day for four days, 15 minims three times on day of experiment; dryness of mouth but no blurring of vision.*

4:00 p. m., ward supper.

8:30, slight pain present.

8:40, atropine sulphate, grain $\frac{1}{75}$, hypodermically.

8:53, stomach emptied by Ewald tube of 530 cc. of gruel; free acid 54, total 92.

9:05, distress less, but still present. Blood sugar 98 mg. per hundred cubic centimeters of blood.

9:08, stomach emptied by Rehfuss tube of 10 cc. of gruel; free acid 20, total 49.

9:10, distress gone.

9:12, 200 cc. of 0.5 per cent hydrochloric acid solution per Rehfuss tube.

9:20, slight pain appeared.

9:22-9:28, 250 cc. of 20 per cent dextrose solution intravenously.

9:58, blood sugar 150 mg. per hundred cubic centimeters of blood.

10:30, pain still present. Stomach emptied of 250 cc. of thin gruel; free acid 83, total 95.

10:40, pain no better. Stomach emptied of 20 cc. of thin gruel; free acid 74, total 97.

10:50, pain gone.

RESULTS OF THE ROENTGENOLOGIC METHOD

As has been stated, the balloon method gives evidence only of intragastric tension, and of the motility and tone of the body of the stomach and of the second and third portions of the duodenum. It gives very little evidence as regards the duodenal cap, the pylorus, and the antrum of the stomach. The other methods described above give only indirect evidence of the conditions present in these regions. Roentgenologic study affords direct evidence of the state of the entire stomach, the pylorus, and the first part of the duodenum.

The results here reported have been corroborated by Dr. C. A. Matthews, roentgenologist of the Cook County Hospital, and by Dr. E. S. Blaine, roentgenologist of the National Pathologic Laboratories and consulting roentgenologist to the Cook County Hospital. Dr. Blaine took several complete sets of plates in his own laboratory as additional evidence.

Twenty-eight normal stomachs were examined with the solution of barium sulphate and 0.5 per cent hydrochloric acid. As a rule, the acid solution produced slightly more spasm of the duodenum than did the neutral solution, but the difference was relatively small. At times, the duodenal cap was as large and well filled with the acid solution as is ever the case with neutral solutions. It was interesting to note the rapid rate at which this solution might be emptied from the stomach in cases of achylia gastrica. This observation furnishes evidence regarding the control of the pylorus and also regarding the hyperperistalsis so commonly noted in these stomachs.

Forty-eight stomachs with ulcer defects were observed with the acid solution. Of these forty-eight, thirty were studied both during the presence of pain and after the pain had been relieved by an alkali. No phenomena were observed during the presence of pain which were not observed during its absence. Frequently the pylorus remained closed for several minutes, but this occurred with the buttermilk barium also and was not accompanied by pain. Gastric peristalsis was very active at times and absent at times, but entirely irrespective of the presence or absence of pain. Similarly, no relationship could be determined between the condition of the cap and the presence or absence of pain, except that in duodenal ulcers pain did not appear until barium passed the pylorus. At one time, in a case of duodenal ulcer, spasm of the entire gastric antrum was noted without pain. At another time, in a sensitive gastric ulcer, spasm of the antrum was noted with excruciating pain, but the pain was also excruciating at other times when no spasm of the antrum was to be seen. The entire lack of relationship between peristalsis, pylorospasm, spasm of the cap, and pain, is well illustrated in the photographs. It must be remembered that while this method gives no evidence of the intragastric tension, the balloon method did afford that information.

In figure 7 there is very little peristalsis evident in either film; the pylorus is open; the duodenal cap is well filled, and a definite niche is seen on the lesser curvature side. The cap is somewhat smaller in the picture taken during the presence of pain than it is in the later one taken after the pain had been relieved by the administration of an alkali. Nevertheless, it is difficult to see evidence here of pylorospasm or of duodenal spasm sufficient to produce pain.

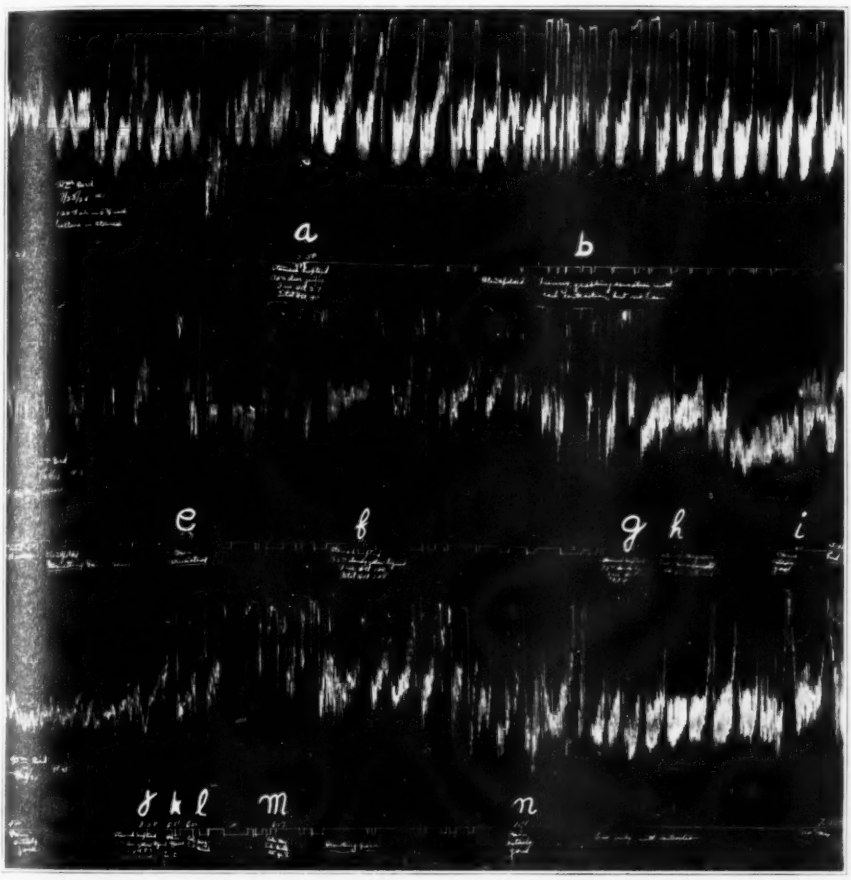


Fig. 7 (experiment 375).—Record of patient with highly sensitive chronically perforated jejunal ulcer, with extensive inflammatory swelling (tracings 2 and 4 omited from consecutive series); the patient was blindfolded, 120 cc. of air in 6¾ inch balloon in stomach: *a*, 2:50, stomach emptied of 30 cc. of clear juice, free acidity 27, total 40; *b*, "funny, grabbing" sensation with each contraction as indicated, but no pain; *c*, 3:56 (not shown), 1.5 mg. of histamine hydrochloride injected subcutaneously; *d*, 4:46 (not shown), pain appeared; *e*, 5:06, pain excruciating—remittent, as indicated; *f*, 5:15, stomach emptied of 185 cc. of cloudy yellow liquid, free acidity 100, total 108; *g*, 5:32, stomach emptied of 75 cc. of cloudy liquid, free acidity 93, total 101; *h*, 5:35, heavy calcined magnesia and sodium bicarbonate, 20 grains (1.3 Gm.) each, given in 60 cc. of water; *i*, 5:44, pain gone entirely; *j*, 6:50, stomach emptied of 95 cc. of clear yellow liquid, free acidity 93, total 100; *k*, 6:51, pain appeared, quite severe, remitting, as indicated; *l*, 6:52, given calcined magnesia and sodium bicarbonate, 10 grains (0.65 Gm.) each; *m*, 6:57, given calcined magnesia and sodium bicarbonate, 10 grains (0.65 Gm.) each; *n*, 7:11, pain entirely gone; contractions now painless.

Figure 8 illustrates the same thing in a case of duodenal ulcer with a much more extensive bulb deformity.

Figure 9 shows a rather inactive stomach, a well filled duodenal cap, and an open pylorus, with a penetrating gastric ulcer. The conditions are nearly the same in the two films, one taken during pain and the other after relief had been obtained by means of an alkali. This patient had very severe pain which was entirely relieved by antacid therapy. During the course of treatment, the defect was observed to diminish in size, and finally it disappeared completely.

In the four parts of figure 10 a similar condition is seen. The cap and pylorus are widely distended during the presence of pain. Furthermore, there is no appreciable difference in the size of the lesser curvature defect in the different roentgenograms, such as one might perhaps expect to find if local spasm were a factor in determining the size of

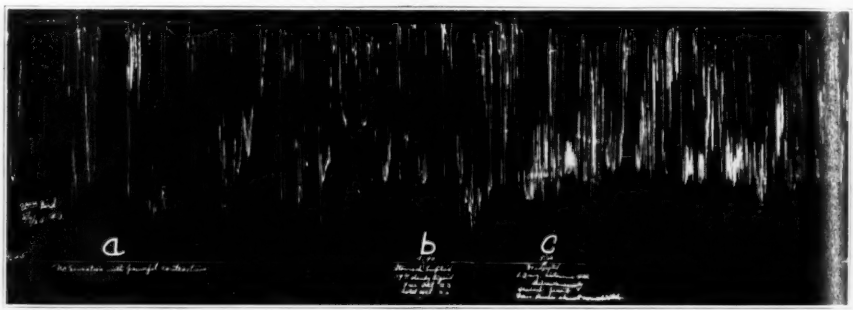


Fig. 8 (experiment 395).—Record of same patient as figure 7 after ten days of intense antacid therapy with 120 cc. of air in 6¾ inch balloon in stomach: *a*, powerful contractions without pain; *b*, 4:40, stomach emptied of 57 cc. of cloudy liquid, free acid 23, total 30; *c*, 5:00, 1.5 mg. of histamine hydrochloride injected subcutaneously; *d* (not shown), pain did not result from the secretion induced by the histamine.

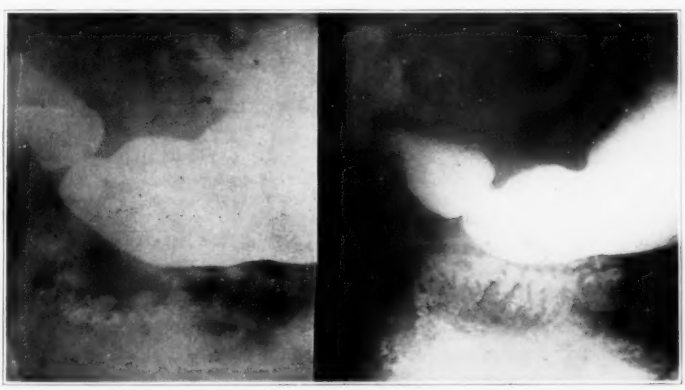
the defect or in the pain. At laparotomy, a penetrating ulcer of the posterior wall of the lesser curvature was found, and a subtotal gastric resection was performed by Dr. Karl Meyer.

COMMENT

It has been shown that the irritant present in the gastric content which constitutes an adequate stimulus to the pain-producing mechanism of a sensative peptic ulcer, namely, hydrochloric acid, does not usually act by means of increased gastric or duodenal tone or motility or by means of pylorospasm. The pain-producing mechanism appears to lie in close relationship to the ulcer. In a relatively small group of highly sensitive mechanisms, the mechanical irritation of normal gastric peristalsis was shown to be an adequate stimulus for either the initiation or

Fig. 9.—Active duodenal ulcer: left, after barium-hydrochloric acid solution, with pain present; right, after alkali, with pain absent.

Fig. 10.—Active duodenal ulcer: left, after hydrochloric acid, with pain present; right, thirty minutes later, after alkali, with pain absent.



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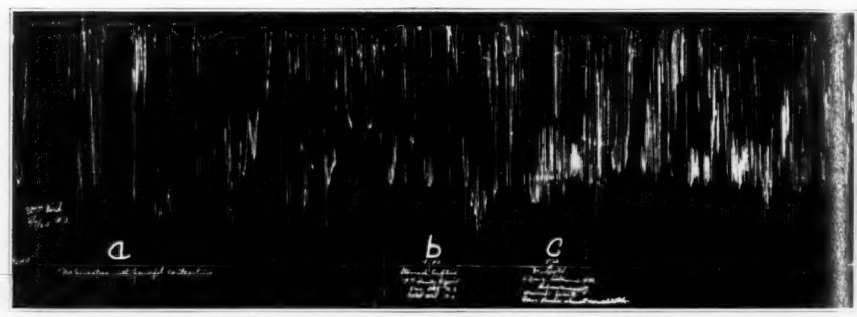

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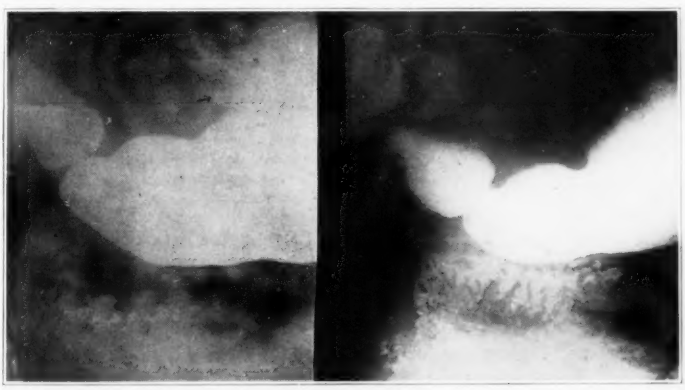

Fig. 11.—Active gastric ulcer: left, after barium-hydrochloric acid solution, with pain present; right, thirty minutes later, after alkali, with no pain.

augmentation of the pain. This effect seemed to be dependent on previous acid sensitization. Some evidence was presented to show that the acid sensitized not only the sensory mechanism, but also the motor mechanism as well. Whether or not these mechanical stimuli may at times constitute adequate stimuli to the pain-producing mechanism in the absence of acid sensitization, has not been determined. I have not had the opportunity of studying an ulcer with true achlorhydria.

The acid may act, presumably, by producing edema in the tissues at the edge of the ulcer, by producing localized muscle spasm or by direct acid irritation of the exposed nerve endings. The problem cannot be decided by the evidence available at present.

CONCLUSIONS

The pain-producing mechanism is intimately associated with the ulcer.

It is not usually dependent on: (*a*) gastric tone or motility, (*b*) duodenal tone or motility, (*c*) pylorospasm.

Under certain conditions, normal gastric peristalsis may constitute an adequate stimulus to the pain-producing mechanism.

Evidence is offered to show that hydrochloric acid may sensitize both the sensory and motor mechanisms.

The rapid emptying of 0.5 per cent hydrochloric acid solutions by stomachs with complete achylia gastrica (pernicious anemia) is noted.

IV. THE PRODUCTION OF PAIN BY THE DISTENTION OF A BALLOON IN THE INTESTINE

During the course of the previous work, occasional attempts were made to produce distress by distention of the balloon at various levels in the intestine. The pressure used was not accurately measured; nevertheless, the results obtained are of interest. It was not difficult to produce distress in this fashion, but it was difficult to gage the intensity of the pain. It would usually come on quickly, and would rapidly become very severe. One of the greatest difficulties encountered was to produce distress of the proper severity for the patient to compare with his ulcer pain. Pains of the same type, due to the same cause, and situated in the same place, may not be recognized as of the same type if there be a great difference in their intensity.

Table 3 is a summary of the results obtained. Distress that was typical as regards type and location, although not necessarily as regards severity, was produced twenty-two times, whereas atypical distress was produced twenty-three times. Most of the tests were made at a time when the ulcer was known to be acid sensitive, but the same results were obtained later when it was found to be insensitive; and in one case, four months after the ulcer and half of the stomach had been

resected. It is particularly noteworthy that in this one case the patient still described the distress produced by distention of the balloon as his old ulcer distress, typical in type and location.

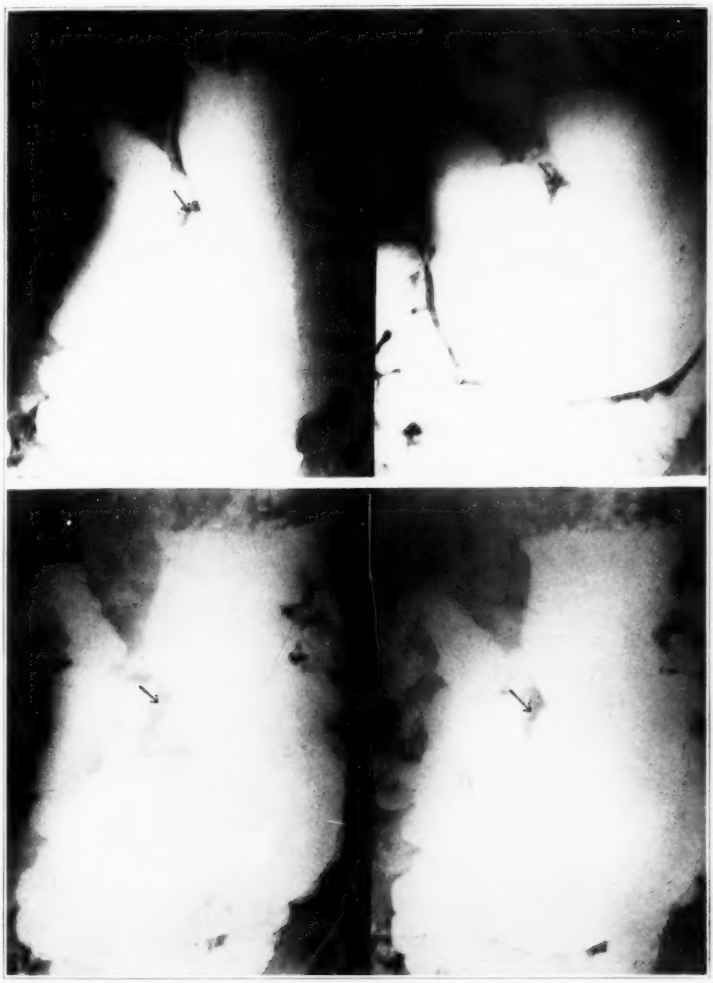

Fig. 12.—Active gastric ulcer: upper left, pain present; upper right, pain absent; lower left, pain present; lower right, pain present.

In view of the fact that it was still possible to produce typical ulcer distress by distention of a balloon in the intestine of patients with acid-insensitive duodenal ulcers and in one instance after resection of the

ulcer, the pain can hardly be interpreted as being due to reflex spasm about the ulcer. The problem of "pain memory" may be involved; nevertheless, these experiments seem to indicate a poor power of localization and differentiation of distress arising from different but adjacent portions of the intestine and produced in different ways.

V. THE PAIN OF GASTRIC CARCINOMA

Certain observations were made during the course of this work on the mechanism of pain in gastric carcinoma. Carcinoma is the only other common gastric ulcerating lesion. Clinically, it may produce pain of identically the same type and location, with the same relationship to food taking and the same relief from emesis, alkalis and eating as that

TABLE 3.—*Distention of the Balloon in the Intestine*

	Gastric	Duodenal	Total
Typical Distress Produced (Number of Times)			
1. When Acid Sensitive			
(a) Pars descendens duodeni	2	10	12
(b) Pars inferior duodeni	2	1	3
(c) Jejunum (first portion)		2	2
2. When Acid Insensitive			
(a) Pars descendens duodeni	—	—	—
(b) Pars inferior duodeni	—	2	2
3. After Resection of Ulcer			
(c) Jejunum (first portion)	—	3	3
Total	4	18	22
Atypical Distress Produced (Number of Times)			
1. When Acid Sensitive			
(a) Pars descendens duodeni	10	5	15
(b) Pars inferior duodeni	4	2	6
(c) Jejunum (first portion)	—	2	2
Total	14	9	23

which characterizes the benign ulcer, or it may produce distress that is entirely different. It varies greatly. It may be made worse by food taking. It may be relieved only partially or not at all by emesis or alkalis. It may be severe and constant, regardless of the nature of the gastric content. These different types of pain in carcinoma may be due to different pain-producing mechanisms. In the following work, an attempt is made to differentiate these factors.

DATA

Table 4 is a summary of the results obtained by means of hydrochloric acid injections as described in part II. The typical pain was initiated or markedly intensified by the injection in eight of the twelve cases. All of the successful results were obtained in patients who had spontaneous distress. In the three patients who had practically no spontaneous pain as a result of their gastric carcinoma, the injection of the acid failed to produce pain. There was one failure in a patient who did have a good deal of spontaneous pain and who had had pain within the preceding twenty-four hours. It is noteworthy, also, that the three

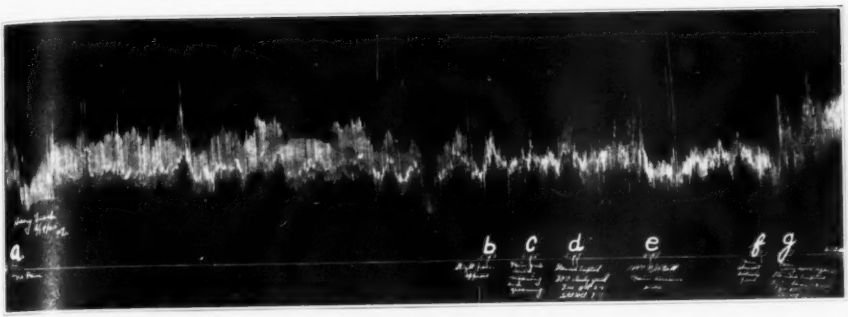

Fig. 13 (experiment 306).—Record of patient with carcinoma of the antrum with 120 cc. of air in 6¾ inch balloon in stomach: *a* (blurred), 5:15, no pain; *b*, 5:43, slight pain appeared; *c*, 5:45, pain quite severe, patient moaning and groaning; *d*, 5:47, stomach emptied of 80 cc. of cloudy gruel, free acidity 24, total 87; *e*, 5:50, pain remained the same; given 100 cc. of tenth normal sodium hydroxide; *f*, 6:07, pain almost entirely gone; *g*, 6:17, pain very severe again; stomach emptied of 85 cc. of cloudy liquid, free acidity 21, total 37.

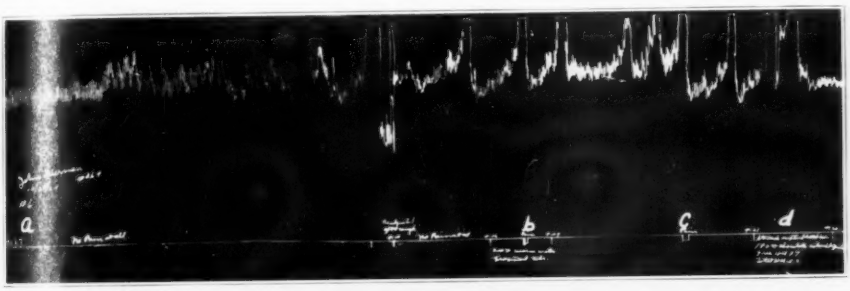

Fig. 14 (experiment 68).—Sixth tracing of patient with carcinomatous ulcer of the stomach (patient blindfolded): *a*, 3:37, good tone but no motility or pain; *b* and *c*, slight twinges of pain—no pain with the other contractions; *d* (blurred), 4:21-4:26, stomach emptied of 180 cc. of chocolate colored liquid, free acidity 17, total 53.

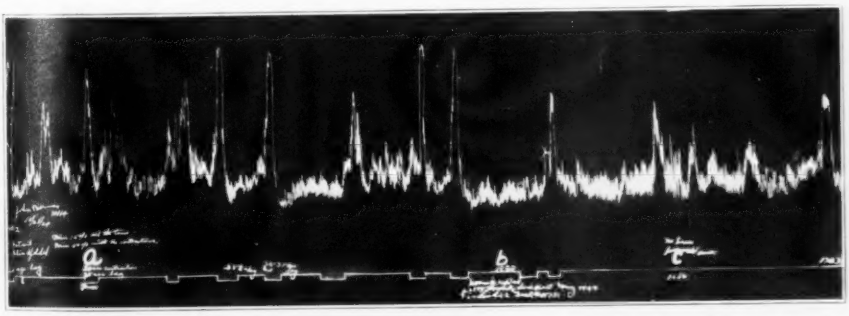

Fig. 15 (experiment 68).—Second tracing: *a* (blurred), 15 per cent of his usual pain continuously, 50 per cent of his usual pain synchronous with the contractions, as indicated; *b*, 12:35, stomach emptied of 315 cc. of chocolate colored gruel; positive benzidine test, free acidity 22, total 102; *c*, 12:52, pain entirely gone; 5:58, pain returned; 6:05, stomach emptied of 25 cc. of cloudy juice, free acidity 35, total 47; 6:10, 200 cc. of twentieth normal sodium hydroxide by Rehfuss tube; 6:17, pain entirely gone; 8:18, 10 cc. of sample of gastric content removed, free acidity 3, total 19.

painless carcinomas occurred in persons whose Ewald test meals contained no free hydrochloric acid. Similarly, patients 1, 3, 4 and 5 were completely or greatly relieved of their pain by antacid therapy. These were the cases with the highest Ewald acidities. Patient 8, with no free acid evident in the Ewald test, obtained almost no relief from antacid therapy, and patient 6, with a low Ewald free acidity, also obtained almost no relief.

TABLE 4.—*Gastric Carcinoma*

Case	Pain	No Pain	Ewald Acidity	Spontaneous Pain	Relief from Antacid Therapy	Remarks
1	1	...	30-70	Severe	Partial	Carcinomatous ulcer resected
2	2	...	20-63	Severe	.....	Extensive carcinoma at laparotomy
3	2	...	40-74	Severe	Complete	Roentgen-ray diagnosis: carcinoma of antrum; died 6 months later
4	1	...	43-63	Severe	Nearly complete	Pyloric carcinoma resected
5	4	...	28-48	Severe	Complete	Massive carcinoma; died 3 months later
6	6	...	15-28	Severe	Slight	Roentgen-ray diagnosis: carcinoma of cardia; died 1 month later
7	1	...	0-70	Severe	.....	Carcinoma with obstruction at laparotomy
8	1	...	0-30	Severe	Slight	Carcinoma of posterior wall found at laparotomy
9	...	1	High	Severe	.....	Roentgen-ray diagnosis: carcinoma of posterior wall
10	...	1	.. ..	Slight	.....	Painless carcinoma of stomach with ascites
11	...	1	0	None	....	Pyloric carcinoma with obstruction found at laparotomy
12	...	1	0-90	None	.....	Carcinoma of pylorus found at laparotomy

The following protocol from case 2 illustrates the production of carcinoma pain by the injection of an acid:

2:55, stomach emptied of 100 cc. of chocolate tinged gruel; free acidity 15, total 28.

3:10, 200 cc. of 0.5 per cent hydrochloric acid solution given by Rehfuss tube. Pain appeared at once, burning and pressing in nature, gradually increasing.

3:20, pain was now more severe than he had ever had.

3:45, pain continued, but was less severe. Stomach emptied of 120 cc. of dark brown liquid; free acidity 120, total 124.

3:54, pain disappeared.

The following protocol illustrates this also, and shows how relatively low acidities may be sufficient to initiate pain in sufficiently sensitive mechanisms.

EXPERIMENT 320.—*Carcinoma of the antrum.*

3:55, stomach emptied of 40 cc. of thick gruel, no free acid (after alkali).

4:05, 200 cc. of 0.25 per cent hydrochloric acid solution given by Rehfuss tube.

4:18, pain appeared.

4:25, pain severe. Ten cubic centimeter sample removed from stomach; free acidity 26, total 62.

4:30, 100 cc. of tenth normal sodium hydroxide given by Rehfuss tube.
4:38, pain entirely gone.
4:57, pain returned; mild.
5:00, stomach emptied of 5 cc. of clear juice; free acidity 18, total 34.
5:36, pain very severe. Stomach emptied of 20 cc. of cloudy juice; free acidity 66, total 79.
5:39, 200 cc. of twentieth normal sodium hydroxide given by Rehfuss tube.
5:45, pain entirely gone.

These protocols show clearly that in certain cases the pain of carcinoma may be initiated by relatively low degrees of gastric acidity and be completely relieved by its neutralization in identically the same manner as that of peptic ulcer.

The tracing shown in figure 11 from patient 5 shows that the pain may be entirely unaccompanied by alterations in intragastric tension or motility.

The opposite type of result is seen in figure 12, patient 1, in which contractions are seen, but pain is not shown, except in two instances when the patient indicated a short intermittent type of pain coincident with two contractions.

Figure 13 from patient 1 shows remittent pain, in which the exacerbations of the pain are synchronous with the gastric contractions. The pain is relieved by emptying the stomach. The patient was blindfolded during this experiment. Here there is remittent pain which is definitely related to the contractions of the stomach.

It is apparent, therefore, that one type of carcinoma pain may resemble the pain of peptic ulcer in that it may be initiated by an adequate degree of free acidity and relieved by neutralization of the acid, and also that in its intermittent and remittent forms it may be initiated or aggravated by gastric peristalsis. There is no evidence here of a constant and continuous type of pain due solely to muscle tension. The best evidence available at present pointing in this direction are the data contained in the following case report:

A woman, aged 50, entered Cook County Hospital, in the service of Dr. Tice, Oct. 24, 1925, complaining of pain in the epigastrium and loss of weight, each of three months' duration. The pain was gnawing in character, usually coming on from one to two hours after eating. It appeared later after heavy meals than after light meals. Eating always relieved the pain. The patient was in the habit of taking two or three crackers to bed with her at night in order to relieve the distress which awakened her. The effect of vomiting and of soda was unknown.

An Ewald test meal showed free acid 0, total acid 10. A second Ewald meal showed free acid 0, total acid 7. A therapeutic aspiration was made at the height of pain; 22 cc. of gruel showed free acidity 0, total 30. The stomach was washed with cold water. Complete relief was obtained in less than ten minutes.

On November 18, Dr. Karl Meyer resected a superficially ulcerating carcinoma of the lesser curvature of the stomach. Grossly and microscopically the tumor was an ulcerating scirrhous carcinoma. The patient made an uneventful recovery.

In this case there was a gnawing epigastric distress, in all probability due to the carcinoma of the stomach, and present without free acid in the gastric content obtained at the time of distress. It seems fair to assume that before coming to the hospital this distress also occurred at a time when there was no free acid in the gastric content, and that, in accordance with the patient's story, it was regularly relieved by the eating of two or three crackers. It seems difficult to explain this distress on any other basis than that of muscle tension or muscular activity.

Another type of carcinoma distress is that which is unaltered by the removal of the irritants in the gastric content, and which is unaltered by those measures which commonly relieve muscle tension temporarily, such as washing out the stomach. This type of pain is usually severe and is present constantly day and night, influenced only by opiates. Fenger [12] commented on this type of pain and considered that it was probably due to malignant infiltration of the nerve fibers.

The distress due to gastric dilatation and distention secondary to pyloric obstruction is scarcely ever a pain and is not included in this consideration of the pain of gastric carcinoma.

The various factors, then, which are known to enter into the production of pain in carcinoma of the stomach are: acid irritation of the pain-producing mechanism, muscle tension and probably malignant infiltration of the nerve fibers.

DESENSITIZATION OF PAIN-PRODUCING MECHANISM

The following case report is of intense interest from the standpoint of the mechanism of pain in both benign and malignant ulcerations of the gastric mucosa:

A man, aged 47, entered Cook County Hospital, in the service of Dr. Carr, June 2, 1925, complaining of a dull aching pain in the epigastrium of two or three weeks' duration, usually occurring about 3 or 4 p. m., lasting until relieved by supper, recurring about 9 or 10 p. m., when it would be relieved by food taking again. At times the pain would be very severe. Physical examination was essentially negative except for a hard firm mass in the epigastrium, about 2 cm. in diameter, and only slightly mobile on respiration. During the weeks the patient was under observation there was a definite increase in the size of this mass.

An Ewald test meal of 75 cc. showed free acidity, 28; total acidity, 48; a motor meal of 40 cc., free acidity, 10; total acidity, 20. The Wassermann reaction was negative. Eleven of fifteen stools gave a positive benzidine test for blood. Roentgen-ray examination showed extensive carcinoma of the pars media of the stomach.

On June 14, 1925, a soft diet was ordered. On June 18, the severe daily pain continued. An acid test produced severe pain (experiment 320). One June 19, the

12. Fenger, Christian: On Cancer of the Stomach, The Collected Works of Christian Fenger, Philadelphia, W. B. Saunders Company, 1912, pp. 126-138.

Sippy treatment was started. The day time relief from pain was immediate and complete. The night pain continued. On June 23, an acid test produced severe pain. On June 24, an acid test produced severe pain.

On July 8, the patient was entirely pain-free, day and night, and was gaining weight. On July 10, an acid test produced slight pain only. On July 14, an acid test of 400 cc. of 0.5 per cent hydrochloric acid solution was given for one hour without distress. On July 17, an acid test of 600 cc. of 0.5 per cent hydrochloric acid solution was given for one and one-half hours without distress. On July 24, the patient was discharged. An operation had been refused.

On August 28, the patient was readmitted for headache and swelling of the feet. The epigastric mass was markedly increased in size. He had remained on management, had gained 27 pounds (12.2 Kg.) in weight, and had been entirely free from pain.

On September 3, he developed right hemiplegia. On September 6, he developed terminal bronchopneumonia. Necropsy was refused.

In short, this was a case of gastric carcinoma with severe pain. The pain-producing mechanism was extremely sensitive to acid. Antacid treatment completely relieved the pain and desensitized the pain-producing mechanism to the extent that 600 cc. of 0.5 per cent hydrochloric acid solution produced no distress in one and one-half hours.

COMMENT

It is a well known fact that many cases of carcinoma of the stomach are relatively painless. Others are extremely painful. The factors responsible for the pain are acid irritation, muscle tension and probably malignant infiltration of the nerve fibers. The pain due to acid irritation may be completely relieved by antacid therapy. The exact mechanism of pain production by means of acid irritation is no better understood in malignant ulceration than it is in benign ulceration. The mechanism of desensitization by antacid therapy is also unknown; an attractive hypothesis is that the checking of the peptic activity prevents the digestion of the slough and of poorly vitalized tissue, and thereby protects the sensitive nerve endings from the action of the chemical irritant.

CONCLUSIONS

Under certain conditions, the pain of gastric carcinoma can be initiated by the introduction of 0.5 per cent hydrochloric acid solution into the stomach, and be relieved by its withdrawal or neutralization.

Muscle tension is at times a factor in the pain of carcinoma.

A third type of pain is apparently due to carcinomatous infiltration of the sensory nerve fibers.

Antacid therapy will completely relieve the pain due to acid irritation, and in some instances give complete relief from the pain of carcinoma.

Antacid therapy may desensitize the pain-producing mechanism so that it is no longer sensitive to 0.5 per cent hydrochloric acid solution.

SUMMARY OF PARTS I TO V

It is shown in part I that the question of achlorhydria in ulcer is not settled as yet. It is fairly well established that the two conditions occur together in rare instances, but the evidence as to whether or not pain is present in such cases is entirely unsatisfactory.

Evidence is offered to show that hydrochloric acid is the irritant normally present in the gastric content which constitutes an adequate stimulus to the pain-producing mechanism of a sensitive peptic ulcer. Other chemical irritants may act in the same way.

It is further shown that this irritant does not usually act by means of increased gastric or duodenal tone or motility, or by means of pylorospasm. Evidence is offered to show that hydrochloric acid may sensitize both the sensory and motor mechanisms. In sufficiently sensitive ulcers, normal gastric peristalsis may constitute an adequate mechanical stimulus to the pain-producing mechanism. In all of the results of this type obtained, acid sensitization seems to have been an essential prerequisite. Whether or not such mechanical irritants may ever be adequate stimuli in the absence of acid sensitization has not been determined, for I have not had the privilege of studying a case of peptic ulcer with true and complete achlorhydria. The possibility that this may occur is suggested by the type of pain seen in the case of frank carcinoma of the stomach reported in which pain was present without free acid and was relieved by the eating of two or three crackers.

It is shown that in certain types of carcinoma pain the same factors are operative as in that of benign ulcer, namely, acid irritation and gastric peristalsis. A third type of carcinoma pain is thought probably to be due to malignant infiltration of the nerve fibers.

The experiments relative to the distress produced by distention of the balloon in the intestines seem to indicate that some persons may be unable to differentiate distress arising in different portions of the intestine and produced in different ways.

The exact mechanism by means of which the acid produces the pain in both benign and malignant ulcerations is not determined. It may act, presumably, by producing edema in the tissues about the edge of the ulcer or by producing very localized muscle spasm, or by direct acid irritation of the exposed nerve endings. It is impossible to decide this question at present, but certain further observations may suggest the truth. The instantaneous production of severe pain which results at times in very sensitive ulcers from the injection of the acid does not argue for the etiologic relationship of gross tissue edema to pain. Certain other characteristics of the pain make it difficult to conceive of its being due to localized muscle spasm. It may come on gradually, being scarcely noticeable at first, and then, by almost imperceptible gradations,

increase in severity to intense pain. It disappears in a similar manner. As the sensitiveness of the pain-producing mechanism decreases, the latent period increases, the severity of the pain diminishes and the pain threshold rises. This occurs in both benign and malignant ulcers. In the benign ulcer, this decrease in the sensitiveness of the pain-producing mechanism seems to be related definitely to the healing process. Carcinomas can scarcely be said to heal, but the methods which desensitize a carcinoma are those which check peptic activity, prevent digestion of the slough and of poorly vitalized tissue, and thereby presumably protect the sensitive mechanism from the action of the chemical irritant. To me these phenomena seem to suggest that the acid may act by direct irritation of exposed nerve endings rather than by the production of localized muscle spasm.

CONCLUSIONS (PARTS I TO V)

Peptic ulcer with true achlorhydria occurs rarely, and the question of the occurrence and type of pain in such cases is unsettled.

Hydrochloric acid is the normal stimulus to the pain-producing mechanism of sensitive peptic ulcers.

Normal gastric peristalsis may be an adequate mechanical stimulus in very sensitive ulcers.

Hydrochloric acid may sensitize both the sensory and motor gastric mechanisms.

No evidence has been found to support the view that hyperchlorhydria may cause typical ulcer pain in the absence of a definite organic lesion of the gastric or duodenal mucosa.

Exact localization and differentiation of different types of enteric pain may be very difficult, if not, at times, impossible.

Under differing conditions, acid irritation and muscle tension may be responsible for all, a part, or none of the pain of gastric carcinoma.

GIARDIASIS IN MAN

ITS PREVALENCE AND RELATION TO DIARRHEA AND TO GALLBLADDER DISEASE *

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Dobell [1] has called attention to the fact that it was Leeuwenhoek in 1861 and not Lambl who discovered this intestinal flagellate of man. Leeuwenhoek discovered the organism in his own stools.

The nomenclatorial status of this flagellate has been a subject for much discussion. For a considerable period it was known as *Lamblia intestinalis* (Blanchard, 1888) in honor of Lambl who rediscovered the organism in 1859; then by *Giardia intestinalis* (Lambl) Alexeieff, 1914, which Dobell believes to be its proper name, and by *Giardia enterica* by Kofoid.[2] In a study of this question made by Boeck and Stiles,[3] the conclusion was reached that *Giardia lamblia*, Stiles, 1915, and first used by Kofoid and Christiansen [4] was the proper scientific name of this intestinal flagellate of man.

MORPHOLOGY

Different species of *Giardia* have been found parasitic in man, dogs, cats, rabbits, rats, mice and frogs, and while they vary from each other chiefly in their size and shape, they all have certain morphologic features in common.

Giardia lamblia of man is a bilaterally symmetrical and binucleate flagellate, measuring from 9 to 21 microns in length and possessing eight flagella, some of which have a portion of their length within the cytoplasm before emerging as free fibrils. The nuclei, two in number, are situated at the anterior end and in the cytoplasm in the bottom of the ventral cup shaped depression or hold-fast organ. The axostyle forms a median midrib running from a central point in the ventral, cup shaped

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1. Dobell, C.: The Discovery of the Intestinal Protozoa of Man, Proc. Roy. Soc. Med. **13**:1, 1920.

2. Kofoid, C. A.: A Critical Review of the Nomenclature of Human Intestinal Flagellates, Cercomonas, Chilomastix, Trichomonas, Tetratrichomonas and Giardia, Univ. Calif. Publ. Zool. **20**:145, 1920.

3. Boeck, W. C., and Stiles, C. W.: Studies on Various Intestinal Parasites (Especially Amebae) of Man, U. S. Public Health Service Hyg. Lab. Bull. 133, Washington, D. C., 1923.

4. Kofoid, C. A., and Christiansen, E. B.: On Giardia Microti Sp. Nov., from the Meadow Mouse, Univ. Calif. Publ. Zool. **16**:23, 1925; On Binary and Multiple Fission in Giardia muris (Grassi), Univ. Calif. Publ. Zool. **16**:30, 1915.

depression posteriorly to the end of the body. The parabasal bodies lie posterior to the ventral depression, dorsal to and across the axostyle. Peristomal fibers border the posterior limit of the hold-fast organ.

The flagellates undergo encystment at some period in their life history. The cysts are ovoid bodies measuring from 10 to 15 microns in length and from 6 to 9 microns in width. Within the cyst are to be seen two or four nuclei, curved parabasal bodies, axostyles and the remains of the intracytoplasmic portions of the posterolateral flagella. These cysts are passed out in the feces and the finding of them is the common method for determining the presence of an infection.

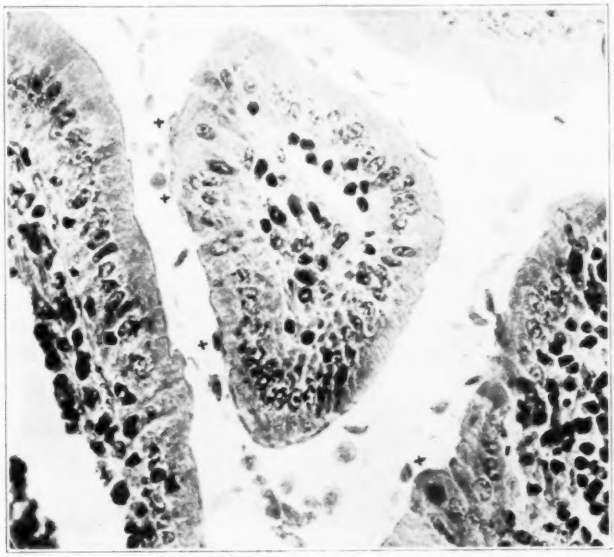

Fig. 1.—Stained section of intestine from the mouse showing Giardia muris either attached (x) to the epithelium or free in the lumen of the crypts; intact epithelial cells with end plates even when flagellates are attached to them, and also the complete absence of all signs of irritation and inflammation, should be noted.

All species of *Giardia* live in the small intestine (duodenum and jejunum) of their host. Sections of duodenum fixed and stained reveal these organisms either attached to the epithelium (accompanying figure) by means of the ventral cup shaped depression or hold-fast organ, or in the lumen of the duodenum and that of the crypts of Leiberkühn. They are obtained in large numbers from man by means of duodenal drainage and they remain alive for a few hours at incubator (37 C.) temperature. *Giardia* has no known forcible means of invading the tissue and it is never found deep in the mucosa of the properly fixed tis-

sues, but the attachment of this flagellate to the epithelial cells has often brought up the question of their pathogenicity.

PREVALENCE

From time to time various investigators and physicians reported finding this protozoan in the human feces. It was found quite frequently in children and was even said to be one of the causes of summer diarrhea, or *Lamblia* enteritis, which was more often observed in the summer season. But little was known of its widespread distribution and the frequency with which it occurred in adults and children until the completion of the numerous protozoan surveys during and after the

TABLE 1.—*Incidence and Infection in Children and Adults*

Investigators	Total Number of Cases Examined		Average Number of Examinations per Case		Total Cases Found Positive for Giardia, per Cent	
	Adults	Children	Adults	Children	Adults	Children
Matthews and Smith (Liverpool cases)[7]	1,098	548	1	1	7.0	14.1
Campbell (Bristol cases)[7]	178	49	2.5	1+	3.9	16.3
M. M. McNutt (Leeds cases)[7]	333	128	1+	1+	3.8	39.8
Maxey [8]	.....	89	...	2.0	....	18.0
Boeck (vide infra)	.....	50	...	2.2	....	22.0
Boeck and Stiles [3]						
a. State prison cases	196	...	1.0	...	2.5	....
b. U. S. Naval Training Station cases	711	...	1.0	...	9.0	....
c. U. S. troops	6,120	...	1.2	...	5.7	....
Kofoid and Swezy,[59] U. S. troops	2,876	...	1+	...	5.9	....
Boeck and Stiles [3]						
Training School A	.....	329	...	5.2	....	14.5
Training School B	.....	83	...	5.5	....	50.6
Matthews and Smith [6]						
Dysenteric convalescents	4,068	...	3.0	...	9.9	....
Same cases	4,068	...	5.6	...	16.4	....
Smith and Matthews,[58] nondysenteric convalescents	450	...	2.0	...	6.0	....

World War by European and American protozoologists. Table 1 gives a summary of some of the observations.

This table reveals the following important facts: (1) that the more examinations one makes per case, the greater will be the incidence of infection, a fact established by Dobell [5] and others, and well illustrated in table 1 by the results of Matthews and Smith [6] on their 4,068 cases of convalescent soldiers; (2) that on the basis of the same number of examinations per case, *Giardia* is more prevalent in children than in adults.

5. Dobell, C.: Reports upon Investigations in the United Kingdom of Dysentery Cases Received from the Eastern Mediterranean; 1, Amebic Dysentery and the Protozoological Investigation of Cases and Carriers, M. Research Commission Special Report, series 4, London, 1917.

6. Matthews, J. R., and Smith, A. M.: The Intestinal Protozoal Infections Among Convalescent Dysenterics Examined at the Liverpool School of Tropical Medicine, Ann. Trop. Med. & Parasitol. **13**:83 (May) 1919.

Dobell [7] is inclined to believe that the statistics do not warrant this second conclusion, i. e., that more children are infected than adults, and he tries to explain the figures on the basis that the evidence of infection, namely, finding the cysts in the stool, occurs more frequently in a given number of stools from children than in the same number from adults and, therefore, that the infection is easier and sooner discovered. But in a previous article [3] I have shown that this does not appear to be the case but that, on the other hand, an infection of *Giardia* is discovered as frequently in adults as in children in a given number of stools. We may conclude, therefore, that more children are infected than adults.

Table 1 shows that the discoverable rate of infection with *Giardia* among adults, on the basis of one examination per case, varies from around 3 to 9 per cent, while among children the rate varies from 14 to 40 per cent. Dobell,[5] however, and subsequently others have shown that one examination per case will discover only from one-third to one-half the actual number of infections that would be found by at least six or more examinations per case, and therefore the actual number of infected cases in any survey based on one examination per case may be estimated at from two to three times the number of discovered cases.

The incidence of infection again varies with the environment and its sanitation. This was well illustrated by Boeck and Stiles [3] for all the intestinal protozoa. Among the children and adults, for example, who live in intimate contact with each other in institutions the hygienic conditions of which are far below standard, a much larger rate of infection occurs than among children in an infirmary or hospital in which there is little personal contact and most desirable hygienic standards are maintained. This is also well shown (table 1) by comparing the rate of infection for the children examined by Miss Nutt (Dobell [7]), of whom the largest number resided in a workhouse and of whom 39.8 per cent were infected, with that of the children in the Johns Hopkins Hospital (Harriet Lane Home) examined by Maxcy [8] and in the Children's Hospital, Boston (table 2), examined by me in July, 1925, of whom 18 per cent and 22 per cent, respectively, were infected with *Giardia*.

It was surprising to learn at what early age children are found infected with *Giardia*. The most astounding and significant results were those of Miss Nutt (Dobell [7]), who examined the feces of twenty-five children of 1 year or less of age and found six of them infected. One child was as young as 3 weeks of age, while the others were 3, 9, 11 and 12 months (two), respectively.

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7. Dobell, C.: A Report on the Occurrence of Intestinal Protozoa in the Inhabitants of Britain, Med. Research Commission Special Report, series 59, London, 1921.

8. Maxcy, K. F.: Giardia (Lamblia) Intestinalis, a Common Protozoan Parasite of Children, Bull. Johns Hopkins Hosp. **32:**166 (May) 1921.

Matthews and Smith[9] found six cases of *Giardia* in seventy-nine children between 1 and 2 years of age. Maxcy found *Giardia* in a girl 22 months of age, and in 17 per cent of the children from 1 to 5 years old, and 40 per cent of those between 6 and 12 years old.

Miss Nutt found the greatest number of infections in children from 1 to 4 years of age, and in the fifty patients examined by me at the Children's Hospital, Boston (table 2), each receiving an average of 2.2 examinations, a similar result was obtained. Of the children from 1 to 5 years old examined at the Children's Hospital, 38.9 per cent were infected, as compared to 16.3 per cent of the children from 6 to 12 years of age. These results are in harmony with those of Matthews and Smith[9] also, but just the opposite to those reported by Maxcy, given in the paragraph above. Maxcy's patients from 1 to 5 years

TABLE 2.—*Incidence, Age and Sex Distribution of Giardia Lamblia Among Fifty Children Examined at the Children's Hospital, Boston (July, 1925)* *

Age	Total, 50		Males, 24		Females, 26	
	Positive	Negative	Positive	Negative	Positive	Negative
2 to 3	2	9	0	4	2	5
3 to 4	2	4	2	4	0	0
4 to 5	2	4	1	2	1	2
5 to 6	2	4	1	2	1	2
6 to 7	1	6	0	2	1	4
7 to 8	0	4	0	2	0	2
8 to 9	2	1	1	0	1	1
9 to 10	0	3	0	1	0	2
10 to 11	0	3	0	2	0	1
11 to 12	0	0	0	0	0	0
12 to 13	0	1	0	0	0	1
Totals	11	39	5	19	6	20

* No other intestinal protozoa were found.

old numbered fifty-five, and those from 6 to 12 years, nineteen, while the 50 patients examined at the Children's Hospital by me were almost equally divided, numbering twenty-nine from 1 to 5 years old and twenty-one from 6 to 12 years old. It seems probable that had Maxcy examined more children from 6 to 12 years old, the incidence would have dropped somewhat and not have been as much as 40 per cent finally. An interesting point still remains in that of the children from 1 to 5 years old examined at the Children's Hospital, more—twice as many—were infected than among a similar group examined by Maxcy in the Johns Hopkins Hospital (Harriet Lane Home). The patients received the same average number of examinations (two), the technic of examination was the same, and the cases were more or less of the same heterogeneous character, the patients coming to the hospital on

9. Matthews, J. R., and Smith, A. M.: The Spread and Incidence of Intestinal Protozoal Infections in the Population of Great Britain: I. Civilians in Liverpool Royal Infirmary; II. Army Recruits; III. Children, Ann. Trop. Med. & Parasitol. **12**:349 (Feb.) 1919.

account of acute infectious diseases, nephritis, diabetes, and other diseases. There seems no satisfactory explanation for the discrepancy in the results of these two surveys.

There were no other intestinal protozoa found in the fifty children examined at the Children's Hospital. This result is singular in itself since other investigators have recorded infections of almost all the other intestinal protozoa. It is quite probable that had more examinations per case been possible, other protozoa would have been found, although even with two examinations per case, one would have expected to have uncovered other infections besides *Giardia*.

DISSEMINATION

The manner by which children acquire infections of *Giardia* is a matter of much speculation. It was thought for a time that rats and mice might serve as reservoirs for *Giardia lamblia*, for the majority of these rodents are to be found infected with a species of *Giardia*. Fantham and Porter [10] tried to prove this point and they apparently succeeded in infecting rats with *Giardia lamblia*, but most of them died. It would appear, therefore, that these animals are not efficient and proper hosts for this intestinal flagellate. Simon,[11] on the other hand, was unable to infect rats with the human *Giardia*, and his studies demonstrated specific differences between *Giardia* of man and rats. He concluded that human giardiasis is of human origin only.

There still remains, however, another side of this problem to be studied before the question of the etiology of human giardiasis can be definitely settled, for while it appears unlikely that the rodents serve as reservoirs for the human *Giardia*, yet it must be proved that man does not get his infection from rodents and that in him the flagellates undergo the slight change in morphology that has resulted in their being classified as a distinct species. Bearing on this point is the failure of Moritz and Hölzl [12] to infect man by feeding cysts of *Giardia* from mice. While this side of the problem will need further experimentation, it is certain, however, that human giardiasis is spread from one person to another by the ingestion of the cysts of the flagellates that occur in the feces. Man may ingest the cysts directly by contamination with feces on his fingers, food or water, or indirectly perhaps through the agency of

10. Fantham, H. B., and Porter, A.: The Pathogenicity of Giardia (Lamblia) Intestinalis to Man and to Experimental Animals, Brit. M. J. **2**:139 (July 29) 1916.

11. Simon, C. E.: A Critique of the Supposed Rodent Origin of Human Giardiasis, Am. J. Hygiene **2**:406 (July) 1922.

12. Moritz, F., and Hölzl, H.: Ueber Häufigkeit und Bedeutung des Vorkommens von Megastoma entericum im Darmkanal des Menschen, München. med. Wchnschr. **39**:831, 1892.

the house fly which may feed on excreta containing the cysts and then deposit them apparently uninjured in its dejecta on food or in drinking water. The cysts live for some time in water or in moist feces, but die shortly on drying. It is very improbable, therefore, that cysts are ever air-borne in a viable state and that dissemination occurs by this route as Musgrave [13] stated. It was demonstrated by Wenyon and O'Connor [14] and Root [15] that the cysts might be ingested by flies and deposited in the feces apparently unharmed.

It is likely that unhygienic conditions in the family, and uncleanliness on the part of parents and others in the family who handle the infant or child, are instrumental in spreading the infection to the baby, for it has been shown by the English investigators that often several members of a family are infected. The crawling, creeping children that are allowed to dirty themselves and remain so, thus encouraging flies to alight on them and their food and drink, or are themselves or their food and drink befouled by contaminated hands are undoubtedly the ones most apt to acquire this infection. Therefore, the observance of proper hygienic measures in the home and in institutions will go far in the prevention of giardiasis.

It seems that some children will later throw off their infection spontaneously; otherwise, the lower rate of infection in adults must be explained in some other manner, for as yet no efficient method of treatment has been discovered.

PATHOGENICITY

Protozoologists and physicians are divided in their opinion in regard to the question of the pathogenicity of *Giardia lamblia* in man. Many take the view that the organism is a harmless commensal and some hold to the other extreme view that it is always pathogenic, while still others maintain the attitude that these flagellates are pathogenic to the extent that they may extend and prolong an already existing pathologic condition because of their activities. It is my purpose in what is to follow to present a critical review and discussion of the evidence that has of late been accumulating and to evaluate this evidence as impersonally and scientifically as best I can. The question of pathogenicity has been raised more especially in cases of gastro-intestinal and chronic gallbladder disturbances.

The clinical manifestations that have been attributed to the presence of *Giardia* in man are (1) diarrhea, persistent or intermittent with inter-

13. Musgrave, W. E.: Flagellate Infestation and Infections, J. A. M. A. **79**:2219 (Dec. 30) 1922.

14. Wenyon, C. M., and O'Connor, F. W.: Human Intestinal Protozoa in the Near East, London, 1917.

15. Root, F. M.: Experiments on the Carriage of Intestinal Protozoa of Man by Flies, Am. J. Hygiene **1**:131 (March) 1921.

vals of constipation; (2) chronic gallbladder disease with symptoms of epigastric or right upper quadrant pain, discomfort or tenderness, dyspepsia, belching of gas, nausea, vomiting and diarrhea, and (3) certain other obscure conditions in which the etiology is not apparent. I will now proceed to examine the evidence that tends to show that these conditions and symptoms occur in persons with infections of *Giardia lamblia*. One must be brief, however, in order to avoid unnecessary length to this article; therefore, only those data will be reviewed that I believe are important to the discussion of this question.

DIARRHEA

Giardia of man has always, except up to the recent era of protozoan surveys, been found most often in diarrheic stools. This was due to the fact that the motile organism was often abundant in such stools and because physicians as a class had not as yet recognized the encysted forms of this flagellate. The inference made was a natural one, *Giardia* must be the cause of the diarrhea, since it was not observed in formed stools, and since "no other cause was found." Various forms of treatment were administered with the result that the diarrhea cleared up, and the flagellates disappeared from the stools; a "cure" was said to have been obtained.

Later on, when the cysts were recognized it was often noted that the infection was still present even after the diarrhea cleared up, for the cysts were found in the formed stools. It was also demonstrated that in infected persons when the cysts occurred alone or even when absent in the feces the motile forms could be brought down by means of catharis, or be obtained by duodenal drainage. It is to be seen, therefore, that the "cures" obtained were only apparent and not real.

During the World War, English protozoologists with physicians had occasion to observe the effect of many kinds of substances in hundreds of cases of infection with *Giardia*, many of which occurred along with *Endamoeba histolytica* or other intestinal protozoa in the same person.

Among the drugs tried were bismuth salicylate, phenyl salicylate, beta-naphthol, guaicol, thymol, turpentine, emetine, calomel, methylene blue, arsphenamine and other arsenicals. Wenyon and O'Connor [14] came to the conclusion "that no satisfactory treatment for lamblia infections exist." This opinion is shared by Dobell and O'Connor [16] and others. In most cases of reported "cure" with eradication of the infection, the individual has not been followed long enough to determine whether the infection is still present or not, but in a few sporadic cases in which this has been done, "cures" appear to have been obtained. In

16. Dobell, C., and O'Connor, F. W.: The Intestinal Protozoa of Man, New York, 1921.

this country Kantor,[17] Simon,[18] Hollander,[19] Carr and Chandler [20] and others reported cases cured by arsphenamine or neoarsphenamine, but Hollander also reported failures in other cases, and this has been the experience of Reed and Wyckoff,[21] and others. The substance has given indifferent results and not universal satisfaction in all cases in which it has been tried (Goiffon and Roux [22] and Cade and Hollande [23]).

The intra-intestinal thermal therapy of de Rivas [24] still awaits confirmation and endorsement by other physicians as an effective method of treating *Giardia* infections.

The question may well be asked, then, does *Giardia* actually cause diarrhea, and if so, how?

In trying to find an answer I may resort either to my own opinions based on isolated cases for evidence for proof or to statistical studies of protozoan surveys covering hundreds of cases. I shall do both to some extent.

STATISTICAL EVIDENCE

The surveys of Matthews and Smith,[9] Maxcy [8] and my present one covering fifty children from the Children's Hospital reveal the fact that generally children under 1 year of age do not become infected with *Giardia*. The only exceptions to these observations are those of Miss Nutt (Dobell [7]), who found six cases of infection among twenty-five infants less than 12 months of age.

From table 3 it may be seen that *Giardia* infections are usually acquired after the first year of life, and increase to a maximum at about the age of 6 or 7, although the incidence is still high in children up to 12 to 16 years of age compared to the adult rate of infection (table 1). Matthews and Smith [9] showed that the rate of infection among 275 children from 1 to 5 years of age was 16.4 per cent as compared to 14.3 per cent among 223 children 5 to 12 years old.

Now, then, if *Giardia* caused diarrhea in children, it would appear from the data in table 3 that diarrhea would be more prevalent among

17. Kantor, J. L.: Lamblia (Giardia) Infection Associated with Cholecystitis, Arch. Int. Med. **32**:693 (Nov.) 1923.

18. Simon, S. K.: Further Observations of Lamblia Intestinalis Infestation and Its Treatment, South. M. J. **15**:458 (June) 1922.

19. Hollander, Edward: Giardia Intestinalis Infection, Arch. Int. Med. **32**:522 (Oct.) 1923.

20. Carr, E. I., and Chandler, W. L.: Successful Treatment of Giardiasis in Man with Neoarsphenamine, J. A. M. A. **74**:1444 (May 22) 1920.

21. Reed, A. C., and Wyckoff, H. A.: Intestinal Protozoa in Clinical Practice, M. Clin. N. Amer. **5**:391 (Sept.) 1922.

22. Goiffon, R., and Roux, J. C.: Les entérites à Lamblia, Arch. d. mal. de l'app. digestif. **9**:601 (April) 1918.

23. Cade, A., and Hollande, A. C.: L'Entérite à "Giardia (Lamblia) intestinalis," Arch. d. mal. de l'app. digestif. **10**:193 (July) 1919.

24. De Rivas, D.: The Effect of Temperature on Protozoan and Metozoan Parasites and the Application of Intra-Intestinal Thermal Therapy in Parasitic and Other Affections of the Intestine, Am. J. Trop. Med. **6**:47 (Jan.) 1926.

children in the age group of 1 to 6 or 7 than among older children and adults. But the fact is that the incidence of *Giardia* infections *actually increases* from year to year in this group of children while the *incidence of diarrhea decreases.*

Another factor must therefore be sought as the cause of diarrhea of infancy and childhood, and this has been definitely known for a long time to be dysentery bacilli as shown by the work of Duvall and Bassett,[25] Flexner and Hall,[26] Davison [27] and Wollstein.[28]

It must be concluded therefore that statistically, at least, Giardia does not appear to be the cause of children's diarrheas. This is borne out by the observations of Matthews and Smith,[9] who state that "the intestinal

TABLE 3.—*Age Distribution of Giardiasis in Children*

	Matthews and Smith [9]		Maxcy [8]		Boeck		Total		
Age	Number Cases Examined	Number Cases Infected	Number Cases Examined	Number Cases Infected	Number Cases Examined	Number Cases Infected	Number Cases Examined	Number Cases Infected	Percentage of Total Cases Examined
0 to 1	50	0	15	0	0	0	65	0	0
1 to 2	70	6	15	1	0	0	94	7	7.4
2 to 3	74	18	12	1	11	2	97	21	21.6
3 to 4	56	9	12	1	6	2	74	12	16.2
4 to 5	66	12	10	4	6	2	82	18	21.9
5 to 6	43	5	6	1	6	2	55	8	14.5
6 to 7	44	10	4	1	7	1	55	12	21.8
7 to 8	36	4	4	3	4	0	44	7	15.9
8 to 9	42	5	2	1	3	2	47	8	17.0
9 to 10	27	4	2	0	3	0	32	4	12.5
10 to 11	23	3	1	0	3	0	27	3	11.1
11 to 12	8	1	4	1	0	0	12	2	16.6
12 to 13	0	0	2	0	1	0	3	0	0
Total.....	548	77	89	14	50	11	687	102	14.8

protozoa are in no way connected with the occurrence of summer diarrhea in children," and by the findings of Maxcy.[8]

My own observations on the fifty children examined at the Children's Hospital were quite similar in character. Diarrhea was a chief complaint in only two cases, one of which had a *Giardia* infection and the other had not. In both these cases the diarrhea was due to an improper diet and vanished when it was changed.

25. Duvall, C. W., and Bassett, V. H.: The Etiology of the Summer Diarrhea of Infants: A Preliminary Report, Am. Med., Philadelphia, **4**:417, 1902. Studies Rockefeller Inst. M. Research **1**, 1904.

26. Flexner, S., and Holt, L. E.: Bacteriological and Clinical Studies of the Diarrheal Diseases of Infancy with Reference to the Bacillus Dysenteriae (Shiga), Studies Rockefeller Inst. M. Research **1**, 1904.

27. Davison, W. C.: Bacillary Dysentery in Children, Bull. Johns Hopkins Hosp. **31**:225 (July) 1920; A Bacteriological and Clinical Consideration of Bacillary Dysentery in Adults and Children, Medicine **1**:389, 1922.

28. Wollstein, M.: A Bacteriologic Study of Acute Diarrhea in Young Children, Am. J. Dis. Child. **25**:310 (April) 1923.

It occurred on three occasions in a diabetic boy (P. S.) 4 years old, following indiscretions of diet. He also had a *Giardia* infection. This boy had a twin brother and a younger sister (3 years) also infected with *Giardia,* but who are developing normally for their age and give no history of intermittent diarrhea. The parents and one other child (18 months) are noninfected.

Diarrhea occurred once in a girl with tuberculous adenitis, but she had no *Giardia* infection.

It was present intermittently in a boy (P. S.) from the time he was 11 months of age until he was almost 4½ years old. He entered the hospital on account of an enlarged abdomen, and following a thorough study of the case a diagnosis of celiac disease was made. The boy was placed on a high protein diet and did very well in the hospital. His abdomen on his first entrance to the hospital, June 25, 1923, measured 25 inches in circumference, and 26½ inches on his last discharge, Jan. 3, 1926. He had grown from 33½ to 37 inches in height, and from 28¼ to 38 pounds (12.8 to 17.2 Kg.) in weight. The diarrhea in this case can be accounted for on the basis of the celiac disease, and when improvement began following the feeding of a proper diet, the diarrhea grew milder and recurred less frequently, and it was entirely absent during the last two and one-half months.

In this small group of cases, it is seen that diarrhea may occur in a decided minority of the children infected with *Giardia,* and as a matter of fact, it may occur almost as frequently in noninfected children. When the diarrhea was significant enough to be made the chief complaint on entry, it was due to an improper diet.

Among children, *Giardia* was said to cause only diarrhea but in adults there is not the same agreement among physicians. For example, Galli-Valerio [29] and others believe that diarrhea alternates with constipation when *Giardia* infections occur in man, but Smithies [30] reports diarrhea only and the complete absence of constipation as a symptom in all his cases, while Hollander [19] states that three of his patients were always constipated and none of them had a history of diarrhea.

When this question of the relation of giardiasis to diarrhea among adults is studied, it is interesting to note that in the examination of the stools of 3,187 American soldiers, of whom 269 stated that they had diarrhea at the time the stools were taken and 2,918 stated that they did not have it, that *Giardia* was present in 6.3 per cent of the group with diarrhea and 5.4 per cent in the group without diarrhea. Again

29. Galli-Valerio, B.: La Lambliase, Rev. méd. de la Suisse Rom. **44**:1 (Jan.) 1924.

30. Smithies, F.: Protoziasis Occurring in Temperature Zone Residents: A Study of 265 Instances with a Discussion of the Associated Digestive Malfunction, Am. J. Trop. Med. **6**:1 (Jan.) 1926.

only seventy-eight cases gave a history of diarrhea or dysentery, while 6,042 did not, and of these *Giardia* occurred in 5.1 per cent of the group with a positive history of diarrhea and dysentery and 5.6 per cent of the group with a negative history (derived from tables 21 and 22, Boeck and Stiles [3]).

This almost identical rate of infection among persons with diarrhea or a history of it, as compared with those who did not have it when the stool was submitted or who had no history of diarrhea or dysentery, appears very significant. It would tend to show that statistically at least, *Giardia* has no relation to diarrhea in adults. The fact that 6,042 men made a declaration of having no history of diarrhea or dysentery as compared with only seventy-eight who did (while the rate of infection among them was practically identical) certainly would tend to show that by and large diarrhea is relatively infrequent in *Giardia* infection. I arrive, therefore, at the same conclusion regarding the relation of giardiasis to diarrhea among adults as I did for children in the foregoing, that statistically, at least, there is little evidence to support the view that *Giardia* causes diarrhea.

How then can I account for the widespread belief among physicians that *Giardia* causes diarrhea in man? The belief has come about as a result of three main factors:

In the first place, as a result of some treatment the physician stopped the diarrhea and thought also he did away with the infection. The accumulation of hundreds of such cases of reported "cures" had the effect of actually convincing some physicians that the flagellates cause the diarrhea. Such evidence, however, is for the most part worthless, for it has been stated above that with the probable exception of a few well controlled cases the "cure" was only apparent since it caused only a cessation of the diarrhea and not an eradication of the infection as subsequent fecal examinations showed.

In the second place, the physician sees patients who are ill and who as a group represent selected cases, in that most of them are either having diarrhea or give a history of intermittent attacks, and when *Giardia* is found in their stools, the etiology of the diarrhea is attributed to this protozoan—no further evidence is often sought. Again, such evidence is entirely biased and tells but a small part of the story for it should be remembered that the well persons harboring *Giardia,* but in whom diarrhea does not occur, do not come into the hands of the physician (as they do in a protozoan survey) and so their infection remains undiscovered. This explains then why most of the physician's patients with *Giardia* infections have diarrhea, or a history of it, and also why in a protozoan survey, more persons have no diarrhea or history of it than persons who do, while the rate of the infection among both is the same.

In the third place, the belief that *Giardia* causes diarrhea is also based on certain data derived from animal inoculation experiments, and on observations of lesions found at postmortem in the human intestine. This evidence has true scientific value, and it is worth while to pass critical judgment on it.

Kanto [17] states that "the facts pointing most strongly to the pathogenic rôle of *Lamblia* (*Giardia*) have been well presented by Fantham and Porter, who found postmortem destructive changes in the intestinal epithelial cells, and by Fairise and Jannin, as well as by Kofoid and Christiansen, who found the parasite embedded in the deeper layers of the intestinal mucosa."

The evidence from these three sources will now be reviewed and also some additional data not mentioned by Kantor.

Fantham and Porter [10] state that they succeeded in infecting kittens and mice, supposedly free of any other species of *Giardia* peculiar to themselves, with *Giardia* from man. Two out of the nine mice were resistant to infection. Some of them developed diarrhea and some did not. Four out of the seven mice infected died. Postmortem observations were as follows: (*a*) erosion of mucous membrane and falling off of whole villi; (*b*) small duodenal ulcers; (*c*) desquamated, epithelial cells in the lumen bearing *Giardia* on them, and (*d*) a condition of generalized inflammation. They concluded that rats may serve as reservoirs of infection for human beings, and that *Giardia* may be conveyed to man from rodents.

It must be obvious to any one who has read the foregoing article of Fantham and Porter that their results do not permit of the conclusions that they draw, but on the contrary, their work suggests that since *Giardia lamblia* infections are so fatal to mice, it would seem most probable that these rodents are not reservoirs at all. Furthermore, they offer no proof that man may get his infection from mice and as stated above, Moritz and Hölzl [12] were unable to infect man with the cysts of *Giardia* found in mice.

Deschiens' [31] results were similar to those of Fantham and Porter, but considerable skepticism now exists regarding these experimental studies since the work of Simon,[11] who was unable to infect either culture or wild rats with *Giardia lamblia*, and none of the rats "showed any signs of sickness, viz., diarrhea." He concluded that human giardiasis was of human origin.

Kofoid and Christiansen [4] reported the observation of *Giardia muris* in the field mouse deep down in the crypts of Leiberkühn, and that these organisms caused "chronic enteritis, especially in young hosts, with

31. Deschiens, R.: Les entérites à Giardia (Lamblia), travail Lab. Parasit. Faculté de Med. Paris, Imprimerie Jehlen, 1921.

inflation and yellowish color of intestine." Boeck [32] stated that in the meadow mouse, *Giardia microti* causes a chronic enteritis accompanied by the erosion of the mucous lining, and the disintegration and falling away of epithelial cells and even of whole villi into the lumen, but there is no gaseous distention. These results are similar to those of Fantham and Porter [10] in their experimental work cited above.

My restudy of the microscopic sections which provided the basis for the foregoing statement regarding the signs of enteritis caused by *Giardia microti* in meadow mice has demonstrated that the evidence cannot be attributed to *Giardia* alone, if at all. New material more carefully fixed immediately after death and then stained shows no evidence whatsoever of enteritis with disintegration and falling away of villi, or any desquamation of epithelial cells beyond what one finds generally. Even the cells on which a flagellate has fastened itself shows no signs of irritation or damage and the secretory activity of the goblet cells is not interfered with (accompanying figure). A small amount of mucus is present in the crypts, but there is no hypersecretion on the part of the epithelium as a result of irritation, such as occurs in amebic colitis. It seems likely, therefore, that my previous observation and those of Fantham and Porter and others can be attributed to poor material, too much manipulation of the tissue, and to postmortem phenomena.

There is so far as I know only the evidence reported by Fairise and Jannin [33] that is based on observations on the human intestine at necropsy. These investigators had a patient who suffered from severe diarrhea for ten months and *Giardia* was found in the stools. They believed that they had satisfactorily ruled out the possibility of intestinal tuberculosis, bacillary and amebic dysentery and worm infection. The case came to necropsy, and a large mamelonated, cauliflower-like growth with ulcerations was found in the cecum, as well as ulcers in the transverse colon and the lower ileum, but no damage was seen in the rest of the small intestine. Microscospic examination of fixed and stained tissues revealed ulcers with necrotic purulent edges, filled with cellular débris. Marked leukocytic infiltration was present, and both motile and encysted forms of *Giardia* were found deep in the mucosa, submucosa and in the muscularis coat whenever an ulcer extended that far.

This evidence is the strongest of any known that tends to incriminate *Giardia* as a true pathogenic parasite of man, but unfortunately the case is obviously not crystal clear. The condition of the duodenum and jejunum, the regular habitat of *Giardia,* was reported normal, while the

32. Boeck, W. C.: Mitosis in Giardia Microti, Univ. Calif. Pub. Zool. **18**:1, 1917.

33. Fairise, C., and Jannin, L.: Dysenterie chronique à Lamblia, étude parasitologique et anatomo-pathologique, Arch. d. méd. exper. et d'anat.-path. **25**: 525, 1913.

flagellates were found in gross lesions outside their normal abode, i. e., the lower ileum, cecum and transverse colon. An explanation is offered here, that the results of examination suggest that this was probably a case of chronic ulcerative colitis, complicated by a cecal ulcerated neoplasm, and that the diarrhea was due directly to these conditions. A marked diarrhea such as this patient had, resulting from irritation and increased peristalsis, was of itself sufficient to bring down the flagellates from the duodenum and some of them became entrapped in the ulcers and crypts of the neoplasm. Here, some of these underwent encystment; they do this normally in the lower ileum and colon. If *Giardia* were solely responsible for the diarrhea and the pathologic findings, it seems strange that no lesions were found in the duodenum and jejunum where the flagellates live in greatest numbers.

In this connection, it may be mentioned that Smithies [30] regards *Giardia* as a secondary invader of ulcers whenever they are present, and that the lesion may be kept open by the flagellates.

Galli-Valerio [29] reported the presence of *Giardia* in a rat and a rabbit dying from diarrhea, but here again since other etiologic factors were not eliminated, there is no scientific evidence for incriminating *Giardia*, for as in the case of chronic enteritis in field mice attributed to *Giardia muris* by Kofoid and Christiansen [4] mere appearances are not sufficient by themselves in the absence of reliable pathologic evidence.

Porter,[34] in South Africa, reported the occurrence of *Giardia* in samples of water "used previously by the parents of native children at the Johannesburg Hospital in preparing food for the infants, identical with those present in the motions of the children." When the food of clean rats was mixed with this contaminated water, the animals contracted diarrhea, passing large numbers of parasites in the feces.

The theories for the production of the diarrhea are manifold, and all as yet without any proof. It is asserted, for example, that the *Giardia*, because of their numbers, irritate the intestinal epithelium and this results in a "catarrhal condition of the mucosa" and often diarrhea if the secretion of mucus is very great. Wenyon [35] stated that "the occurrence of repeated attacks of diarrhea with a certain degree of abdominal uneasiness preceding the attacks and the passage of such extraordinary numbers of flagellates, especially in the mucus, leads me to suspect that sometimes, at any rate, *Giardia intestinalis* may produce sufficient irritation of the small intestine to justify us in regarding it as pathogenic." But, to date, I know of no pathologic evidence gained from a study of stained sections of the intestine that lends any proof to this idea, and

34. Porter, A.: A Survey of the Intestinal Entozoa . . . Observed Among Natives in Johannesburg, Memoirs South African Instit. M. Research, no. 11, 1919, p. 39.

35. Wenyon, C. M.: Observations on the Intestinal Protozoa; Their Diagnosis and Pathogenicity, Lancet **2**:1173, 1915.

clinical evidence alone is not sufficient since other factors alone or associated with the presence of the *Giardia* might produce the irritation and diarrhea. The same mucoid type of diarrhea, minus the flagellates, may be seen at times in uninfected persons.

Smithies [30] offers as an explanation of the diarrhea the suggestion that the diarrhea represents a toxic manifestation dependent on the absorption of poisonous amines which have resulted from a splitting of dead protozoa and bacteria, or of food proteins by the action of bacteria, which he believes are unusually abundant in stools that contain protozoa. In support of this idea, he states that the administration of substances that "sharply decrease the degree of bacterial activity in the intestine and yet have little or no effect upon protozoa" changes the physical characteristics of the stool and the "diarrhea is ameliorated or ceases."

It will be difficult to obtain proof for or against this theory until more is known of the constitution of the protozoan body and its fate after death. The supporting evidence cited by Smithies hardly touches the case, however, for it would be only in cases of achylia gastrica for the most part that a rich bacterial flora would occur in the duodenum, jejunum and upper ileum (the zone of rapid absorption and the habitat of the flagellates) and there cause the protein splitting of the dead *Giardia* and bacteria, for normally the bacteria are most prevalent in the large intestine beyond the habitat of *Giardia*. Again, if certain drugs affect the bacterial activity, and at the same time not the protozoa, so as to cause a disappearance of the diarrhea, it seems likely that in most cases the effect of the drug was not manifested until it reached the large intestine, where the bacteria predominatae, and we could as justifiably draw the conclusion that the diarrhea was probably of bacterial origin from fermentative and putrefactive processes acting on material in the colon, as to attribute it to the protozoa living high up in the small intestine. Smithies [30] stated that it is not possible to attribute the diarrhea to disturbed gastric secretory function, for in one third of his cases of *Giardia* infection the gastric values were normal.

A general criticism that seems to apply to all claims that *Giardia* is pathogenic and causes diarrhea, symptoms of abdominal pain, tenderness, nausea and vomiting is that, clinically, no characteristic symptomatic onset has been described that would suggest the beginning of the infection or the pathologic process, should the latter not coincide with the date of infection. The diarrhea due to improper feeding of infants, or to dysentery bacilli in children and adults, has a typical onset as to time, signs and symptoms. In infections of *Giardia*, however, the time of the acquisition of the infection is unknown to the host since he is unaware of any characteristic symptoms.

Let us now consider the relationship of *Giardia* infections to disease of the gallbladder.

GALLBLADDER DISEASE

Disease of the gallbladder is often dependent on infections of the gastro-intestinal tract. This fact has been demonstrated by the experimental studies of Grieg,[36] Nichols,[37] Parker and Franke,[38] and Meyer, Nelson and Feusier,[39] for infections of typhoid, paratyphoid A and B, dysentery and cholera bacilli. Recently, the review of Soper[40] shows that this relationship also extends to other infections as well. In 411 cases of gallbladder disease, it was found that in 121 cases there was a history of puerperal infection while the origin was obscure or unknown in 120 other cases, but a definite relation to gastro-intestinal infections existed in the remaining 170 cases. Twenty-two per cent gave a history of typhoid; 10 per cent, dysentery; 17.6 per cent purulent proctosigmoiditis; 7 per cent, chronic ulcerative colitis; 20 per cent, chronic catarrhal colitis; 7 per cent, colonic diverticulitis, and 15 per cent had gastritis anacida.

Many physicians, especially many of the gastro-enterologists, have come to believe that *Giardia* infections are also related to the causation of gallbladder disease. It is believed that the flagellates may either initiate the disease process in the gallbladder by their migration from the duodenum or that they may play the part of a secondary invader and prolong an already existing cholecystitis of probable bacterial origin.

Smithies[41] reported the presence of viable *Giardia* in the contents of the gallbladder removed at operation from a man with acute symptoms of gallbladder disease. This observation was a most important one and it demonstrated that under certain pathologic conditions, *Giardia* does obtain entrance to the gallbladder and may remain viable in the concentrated bile of this organ.

Subsequently, the belief in the probability of *Giardia* causing cholecystitis grew tremendously as a result of the extensive and common practice of the Meltzer-Lyon method of drainage of the biliary tract

36. Grieg, E. D. W.: An Investigation on the Occurrence of the Cholera Vibrio in the Biliary Passages, Indian J. M. Research **1**:44, 1913-1914; Lesions of the Gallbladder and Biliary Passages in Cholera, ibid. **2**:28, 1914-1915.

37. Nichols, H. J.: Experimental Observations on the Pathogenesis of Gallbladder Infections in Typhoid, Cholera and Dysentery, J. Exper. Med. **24**:502, 1916.

38. Parker, J. T., and Franke, E.: The Fate of Typhoid Bacilli Injected Intravenously into Normal and Typhoid Immune Animals, J. M. Research **39**:301 (Jan.) 1919.

39. Meyer, K. F.; Neilson, N. M., and Feusier, M. L.: A Comparative Study of the Infections Produced by Intravenous Injections of Typhoid, Paratyphoid A and B Bacilli in Normal and Immunized Rabbits, J. Infect. Dis. **28**:408 (May-June) 1921.

40. Soper, H. W.: Relationship Between Disease of the Gallbladder and Infection in the Gastro-Intestinal Tract, Ann. Clin. Med. **4**:422 (Nov.) 1925.

41. Smithies, F.: Tr. Am. Gastro-Enterological A., 1925.

with a duodenal tube and the administration of magnesium sulphate. *Giardia* was occasionally found by this means in the fasting contents of the duodenum, and in the B fraction (supposedly coming from only the gallbladder). What seemed more important was the finding of the flagellates at times in the B fraction when they had not been found in the duodenal contents before the administration of the magnesium sulphate. Such observations were recorded by Knighton,[42] Hollander,[19] Labbé, Nepreux and Gavrila,[43] Lyon and Swalm [44] and others. These observations were interpreted to mean (1) that *Giardia* may ascend the common and cystic ducts and reach the gallbladder, and (2) that they might be present in the gallbladder while absent from the duodenum and thus be in a position in which they could bring about reinfection of the duodenum, should the latter be free following treatment.

It will be observed that with the exception of the case cited by Smithies in which *Giardia* was actually found in the gallbladder removed at operation, the only evidence suggesting that this flagellate may live in this organ is its occurrence in the B fraction of the bile, for *Giardia* has not been observed in any other gallbladders removed at operation, even in cases in which the flagellates were known to be present in the duodenum (Simon,[18] Silverman, in Simon,[18] and Lyon and Swalm [44]).

Evidence, however, that is based on the observation of *Giardia* in the B fraction of the bile during biliary drainage is not dependable. It is not dependable because the source of the B bile cannot be attributed to the gallbladder alone for it may come from the liver directly.

Bile in the B fraction in the Meltzer-Lyon test is recognized by its darker color as compared to that in the common hepatic duct and flows as a continuous stream for some time after magnesium sulphate has been given. Bile of the same color, however, has been obtained in cases in which the gallbladder was prevented from emptying its contents following the administration of magnesium sulphate because of a blocking of the cystic duct by a stone [45] or even in the absence of the gallbladder when hepatitis probably was present, as reported by Dunn and Connell [46] and others. Likewise, when dyes were injected into the gallbladder,

42. Knighton, J. E.: Lamblia Intestinalis, with Report of Cases, South. M. J. **15**:457, 1922.

43. Labbé, M.; Nepveux, F., and Gavrila: Lambliasis of the Gallbladder, Bull. Soc. méd. d. hôp. de Paris **49**:1505, 1925.

44. Lyon, B. B. V., and Swalm, W. A.: Giardiasis: Its Frenqency, Recognition, Treatment and Certain Clinical Factors, Am. J. M. Sc. **170**:348 (Sept.) 1925.

45. Einhorn, M.: Action of Various Salts and Other Substances on the Liver After Their Introduction into the Duodenum, New York M. J. **114**:262 (Sept. 7) 1921.

46. Dunn, A. D., and Connell, K.: A Report of a Case of Hepatoduodenostomy, J. A. M. A. **77**:1093 (Oct. 1) 1921.

B bile was obtained, but none of the dye was present in it.[47] The color of bile alone, therefore, does not indicate the source of the bile, and because of this fact it is important to consider the character of the sediment also in ascertaining where the bile comes from. Jones,[48] however, obtained bile that appeared like B bile, and was identical with it as determined by spectroscopy, in a patient in whom the gallbladder previously had been removed.

A number of investigators, Crohn, Reiss and Radin,[49] Johnson,[50] Harer, Hargis and Van Meter [51] and others did not obtain a contraction and emptying of the gallbladder following the administration of magnesium sulphate. Silverman and Menville,[52] Sosman, Whitaker and Edson [53] and Whitaker,[54] however, by means of cholecystography have shown that the gallbladder shadow becomes smaller after magnesium sulphate has been given intraduodenally, and they have interpreted this to be due to the contraction of the gallbladder. The gallbladder does not empty itself completely and this is in accordance with the work of Johnson,[50] who found that one could repeat the Meltzer-Lyon test four times within forty to sixty minutes and obtain B bile each time.

The more recent investigations of Boyden [55] and Whitaker and Boyden [56] have demonstrated that although the gallbladder does empty partly after administering magnesium sulphate, a much better result with complete emptying of the gallbladder brought about by rhythmic contractions of its musculature is obtained following a lipoid meal of egg yolk and cream.

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47. Crohn, B. B.; Reiss, J., and Radin, M. J.: Experiences with the Lyon-Meltzer Method for the Diagnosis of Gallbladder Disease, J. A. M. A. **76**:1567 (June 4) 1921. Diamond, J. S.: An Experimental Study of the Meltzer-Lyon Test, with Comment on the Physiology of the Gallbladder and Sphincter Vateri, Am. J. M. Sc. **166**:894 (Dec.) 1923.

48. Jones, C. M.: The Rational Use of Duodenal Drainage, Arch. Int. Med. **34**:60 (July) 1924.

49. Crohn, Reiss and Radin (footnote 47, first reference).

50. Johnson, W. O.: The Function of the Gallbladder, with Special Relation to the Meltzer-Lyon Test, Surg. Gynec. Obst. **34**:177, 1922.

51. Harer, W. B.; Hargis, E. H., and Van Meter, V. C.: Studies of the Function of the Gallbladder, Surg. Gynec. Obst. **34**:307 (March) 1922.

52. Silverman, D. N., and Menville, L. J.: Observations of Visualized Gallbladder by the Graham Method, with Reference to the Effect of Nonsurgical Biliary Drainage: Preliminary Report, J. A. M. A. **84**:416 (Feb. 7) 1925.

53. Sosman, W. C.; Whitaker, L. R., and Edson, P. J.: Clinical and Experimental Cholecystography, Am. J. Roengenol. **14**:495-503 (Dec.) 1925.

54. Whitaker, L. R.: Experiences with Cholecystography, J. A. M. A. **86**:239 (Jan. 26) 1926.

55. Boyden, E. A.: The Effect of Natual Foods on the Distention of the Gallbladder, with a Note on the Change in Pattern of the Mucosa as It Passes from Distention to Collapse, Anat. Rec. **30**:333, 1925; Observations on the Physiology of the Gallbladder, abstr., Am. A. Anat. Rec. **32**:202 (March) 1926.

56. Whitaker, L. R., and Boyden, E. A.: Observations on the Function of the Gallbladder, Am. J. Physiol. **76**:199 (March) 1926.

As a result of these studies, we may conclude that the gallbladder does contract following magnesium sulphate and that B bile does come from this organ, but it should be remembered that bile of the same color and constitution may be obtained in some cases of cholelithiasis with cholecystitis, or in persons who have no gallbladder. It is presumed that in these cases, the dark bile comes directly from the liver. Since the source of the B bile cannot be attributed to the gallbladder alone with certainty in all cases, it would appear to be illogical to assume that presence of *Giardia* in this particular fraction of the bile constitutes proof that they have come from the gallbladder.

How then is the occurrence of *Giardia* in the darker bile to be explained when it was absent in the duodenal fasting contents? Hollander [19] often found that following the injection of hypertonic salt solutions the flagellates occurred in flocculi from the duodenal crypts when none had been seen in specimens of the duodenal fluids. This may be explained, I believe, by the action of the salt solution on the intestinal mucosa. Magnesium sulphate as employed in the Meltzer-Lyon test is an irritant to the intestinal mucosa and causes an increased secretion of mucus, and because of its hypertonicity it also results in an extraction of water from the same tissues. This action of the salt results in an increased flow of fluid out of the glandular crypts carrying the flagellates with it into the lumen of the duodenum.

I have also observed that a continuous flow of fluid (from 5 to 15 cc.) lighter in color than that previously dropping into the flask occurred a few minutes after the administration of from 25 to 30 cc. of warm water through the duodenal tube. This lighter colored yellow fluid also contained fewer flagellates and when the bile resumed its deeper, golden yellow again the flagellates were present in increased numbers also. No continuous flow of dark bile (B) was obtained. This result was explained by supposing that some of the warm water was regurgitated as a result of a wave of reverse peristalsis in the duodenum and when the water reached the region of the tip of the duodenal tube, the duodenal contents became diluted, resulting in a lighter colored fluid and fewer flagellates per unit volume of contents. The flow became continuous because of the increase in pressure and larger amount of fluid in the particular area brought about by the wave of peristalsis. This explanation is in accord with Johnson's [50] observations that the sphincter of Oddi failed to respond to stimulation with water.

More observations, however, are necessary before adequate proof can be had for this explanation, but it must always be considered probable that failure to find *Giardia* in the duodenal fasting contents and only in the B fraction can be reasonably explained either as Hollander has done, by showing that the hypertonic salts apparently cause the *Giardia* to come out of the crypts as explained above, or by the carriage of the flagellates from a lower duodenal or jejunal segment upward to

the area of the duodenal tip, as a result of a reverse wave of peristalsis, and there the organisms mix with the outflowing B bile.

We may conclude, therefore, that the evidence furnished by duodenal drainage is not reliable proof that *Giardia* normally ascends the common and cystic ducts to live in the gallbladder. The only evidence that is conclusive is the actual presence of these flagellates in the gallbladder, but the single case observed by Smithies is hardly sufficient, for even in this instance it is not clear that *Giardia* caused any damage. Its entrance in this one case may have been gained as a result of a dilated exit of the common duct in the papilla of Vater brought about by an antecedent pathologic condition.

The presence or absence of a preexisting pathologic process must be determined in all cases, for on the observations depends the solution of the question whether *Giardia* by itself may cause chronic gallbladder disease or only be of the nature of a secondary invader.

Lyon and Swalm [44] pointed out that among 798 persons, in 80 per cent of whom gall tract disease was recognizable, *Giardia* occurred in only twenty cases, an almost insignificant proportion. They and others, however, did not obtain *Giardia* from gallbladders removed at operation, as reported by Smithies in one case.

If the migration of *Giardia* to the gallbladder were not preceded but were followed by pathologic changes, then it would appear probable that the initial damage could be attributed to the flagellates, the picture later on becoming complicated by bacterial infection as well. This view, however, does not seem probable on the basis of the data available for the following reasons: (1) because gallbladder disease is much less frequent in children than in adults, although a larger proportion of children are actually infected than is the case with adults; (2) many, if not most of the cases of chronic cholecystitis are of bacterial origin, and (3) in gallbladder disease as well as in diarrhea, by far more persons are infected with *Giardia* and have no symptoms and therefore are not seen by the physician than there are those who do. This may be seen by observing the greater rate of infection for *Giardia* in children and adults (table 1) as compared to the incidence of gallbladder disease that is attributed to or associated with an infection with *Giardia*. In Lyon and Swalm's [44] series, the latter incidence was around 3 per cent (80 per cent of 798 cases showed findings of cholecystitis, of which twenty had *Giardia*).

It is likely from the present data that *Giardia* does not ascend the common and cystic ducts and reach the gallbladder except in rare instances, but is confined normally to the duodenum and upper jejunum. Its entrance into the biliary passages and then the gallbladder, as was found in the case cited by Smithies, would appear probably dependent

on antecedent disease involving the sphincter of Oddi in the papilla of Vater, so as to cause a temporary or permanent dilatation of the end of the common duct, and thus allow the migration of the flagellates up this passage and the cystic duct into the gallbladder.

The occurrence of such lesions must be rare, however, in acute chronic gallbladder disease because the removal of the gallbladder is generally followed by a complete and permanent disappearance of the symptoms, even in the few cases noted thus far that have shown duodenal infection with *Giardia* previous to and after the operation. Cholecystectomy does not rid a person of his intestinal infection with *Giardia* and this is what might be expected since the duodenal environment in which the protozoa live is not altered physiologically by the absence of the gallbladder. This was well illustrated in the case of the small diabetic boy, referred to in a previous portion of this article, who developed cholecystitis when he was 3½ years of age.

The history of this 4 year old boy's illness is very interesting in that it shows how early gallbladder disease may occur in the life of a diabetic child, and it permits of speculation as to the rôle played by *Giardia* in the production of the cholecystitis.

This boy had an acute attack of diarrhea following the eating of watermelon at the age of 15 months and three weeks later developed diabetes mellitus. He entered the Infant's Hospital, July 31, 1923, and since that time he has spent most of his life in the Infants' and Children's Hospitals. Since September, 1925, he has been at the Boston City Hospital (Thorndike Memorial Laboratory). While in these hospitals he was not troubled with diarrhea except on one occasion in the Infants' Hospital. He ran a swinging temperature (except for a period of eleven days) from 97 to 98 in the morning to 99 to 100 in the afternoon with periodic elevations above 100 to 102; it once reached 106, when the attack of diarrhea occurred. His white count was always elevated from 16,000 to 18,000. He was negative for both Shick and tuberculin tests. Acute diarrhea for a day occurred once more in August, 1925, just before his last entrance to the Children's Hospital, probably as a result of breaking away from his prescribed diabetic diet.

In the Boston City Hospital, his temperature behaved in the same way as before, and his white count was always elevated and as high as 29,500. He became definitely jaundiced, Oct. 25, 1925, and tender in the upper right quadrant. Subsequently gallbladder roentgenograms were made on three occasions, the dye being given by mouth once and intravenously twice, and no shadow appeared. A cholecystectomy was done. The microscopic examination revealed evidence of chronic cholecystitis. Following the operation the child's temperature ran along normally for the first time; likewise, his white count became normal, and his diabetic condition, much improved. Examination of the gallbladder, microscopically, failed to show any *Giardia* present. Fecal examinations revealed the presence of the cysts, however, so the operation did not clear up the flagellate infection. There have been no attacks of diarrhea during his entire stay in the Boston City Hospital thus far (ten months). The *Giardia* infection has persisted since the operation, but the swinging temperature, elevated white count, and symptoms of pain, tenderness and jaundice disappeared completely, and have not recurred.

Some clinicians would probably have attributed the cholecystitis in this diabetic boy to the *Giardia* infection, merely because it was a complicating feature, but this interpretation does not seem warranted in view

of the absence of the flagellates in the removed gallbladder, the complete disappearance of symptoms following the operation, and the persistence of the *Giardia* infection in the duodenum. It seems more probable that the cholecystitis may possibly have originated from a duodenitis of bacterial origin at about the time the patient developed diabetes and that an extension of the inflammatory process or infection to include the gallbladder occurred. In this organ, the disease process developed and persisted even after the duodenitis had subsided. Whether or not *Giardia* may have had anything to do with the duodenitis and the extension of the infection is a matter of speculation, but to me it appears most unlikely since gallbladder disease is so uncommon in children as compared to the incidence of *Giardia* infection, and since the boy became symptomless after the operation.

The boy's twin brother and a 3 year old sister are also infected with *Giardia*. To date, however, there is no history of a sharply defined onset characterized by an acute gastric upset followed by irregular temperature, leukocytosis and the development of diabetes mellitus, such as their brother had; in fact, the children have enjoyed normal development thus far and have led no one to suspect that they too had a *Giardia* infection. These cases appear to offer "control" evidence that *Giardia* infections are not etiologically related to gallbladder disease.

The duodenum being the normal habitat of *Giardia*, they are located favorably for playing a part in the production of gallbladder disturbances but, if they do, the exact mechanism by which they enter the biliary tract and produce disease has not been discovered, and the present evidence that seeks to convict these protozoa of causing disease of the duodenum and gallbladder is meager, for the most part unscientific and unconvincing. We are in need of controlled evidence based on experimental and pathologic studies before we can definitely state that *Giardia* reaches the gallbladder or other organs sufficiently often (if at all) to be a factor of importance in the etiology of cholecystitis, and whenever it is found there it should be determined whether it is a primary cause of gallbladder disease or only a secondary invader that has gained access to the biliary tract because of antecedent disease involving the papilla of Vater.

ARTHRITIS DEFORMANS, NEURESTHENIA, MELANCHOLIA, ETC.

Barrow [57] and others have attributed the etiology of arthritis deformans, and various poorly defined and obscure states of ill health, referred to as neurasthenia, melancholia and dyspepsia and characterized by symptoms of nausea, belching of gas, epigastric or generalized abdominal pain and tenderness, loss of "pep" and weight, to *Giardia* (and other intestinal protozoa) whenever this infection is found. No

57. Barrow, J. V.: A Clinical Study of the Intestinal Protozoa, Based on Seven Hundred and Twenty-Five Cases, Am. J. Trop. Med. **4**:23 (Jan.) 1924.

evidence, however, was furnished that is scientific and convincing, but only conjectures of theoretical value were made. At present, therefore, it seems unlikely that *Giardia* is an etiologic factor in the causation of these conditions.

SUMMARY

Giardia infections occur more often in children than in adults, and the incidence of infection is remarkably high in children from 1 to 7 years of age. The infection appears to be acquired, as a rule, after the first year of life.

Giardia is said to cause recurrent diarrhea in children, and diarrhea only or diarrhea alternating with constipation in adults. Diarrhea in young children is more frequent than in older children and adults, but this is due to the fact that most cases are due to improper feeding or to colitis due to dysentery bacilli.

In children and adults as a whole statistical studies indicate that diarrhea does not occur any more frequently in those persons infected with *Giardia* than among noninfected persons.

The belief among physicians that *Giardia* causes diarrhea appears to be due to three factors: (*a*) numerous reported "cures" are now known to be in most cases without basis of fact; (*b*) reported cases of diarrhea and "cure" by physicians on a group of selected, sick persons complaining of diarrhea at the time or in the past; such evidence is one-sided for the well persons with *Giardia* infections do not come under the physician's care but are seen and examined in protozoan surveys that by the very nature of things do not include such an exclusive selection of persons; (*c*) animal inoculation experimentation and the observation on material obtained at necropsy of man infected with *Giardia* are cited as evidence, but a review of the data shows the evidence to be either meager and devoid of proper control measures or open to other and as logical interpretations. They are at best quite inconclusive and demanding of more confirmatory observations.

There appears to be no specific symptomatic onset that characterizes infections of *Giardia* clinically.

If we weigh the evidence at hand, there is little in the way of scientific proof that indicates *Giardia lamblia* itself causes diarrhea in either children or adults, except perhaps in a few obscure and sporadic cases, and as much or more evidence, some of it statistical and some pathologic in character, that indicates that this protozoon does not cause diarrhea. It remains to be proved, however, whether *Giardia* might influence temporarily an existing affection, viz., duodenitis or colitis of bacterial origin which causes or aggravates a diarrhea already present. The evidence pointing to this possibility is totally lacking at present, and all discussions constitute only theoretical speculations.

The finding of viable *Giardia* in the gallbladder following its removal has been reported only in the single case of Smithies. The occurrence

of this flagellate in the B fraction of the bile obtained by the Meltzer-Lyon method of duodenal biliary drainage does not of itself constitute evidence of invasion of the biliary passages, even in cases of chronic cholecystitis. The conclusions reached by various gastro-enterologists that *Giardia* may either cause chronic cholecystitis or secondarily complicate this condition appear to be based on inadequate evidence.

The data at present available indicate that *Giardia* does not initiate any pathologic changes and it is questionable whether it in any way tends to aggravate, prolong or extend preexisting inflammatory conditions of duodenum or gallbladder. This conclusion is deduced from the following facts: (*a*) *Giardia* up to the present time has been found in only one instance in the gallbladder removed at operation; (*b*) while in children gallbladder disease is extremely rare, the rate of *Giardia* infection is two or three times as great as in adults in whom cholecystitis is comparatively frequent; (*c*) *Giardia* infections occur infrequently in persons with disease of the gallbladder, which is, however, frequently a result of gastro-intestinal (bacterial) infection; (*d*) the symptoms of cholecystitis are cleared up by cholecystectomy, but when associated with *Giardia* this organism may persist after operation; (*e*) *Giardia* infections may occur in several members of the same family but cholecystitis does not occur in all of them and may never appear.

The rare entrance of *Giardia* to the biliary tract is probably dependent on a lesion in the papilla of Vater involving the sphincter of Oddi and causing a dilatation of the end of the common duct. Such a lesion might allow both bacteria and *Giardia* to ascend to the pancreas, gallbladder and liver and in such instances it seems more probable that any resulting disease condition would be better attributed to the bacterial invasion than to the migration of the protozoa, since the latter produce no demonstrable lesions in the duodenum.

It has not been shown as yet how *Giardia* may produce any disease and the mechanism by which it obtained entrance to the biliary tract in the single case reported still remains obscure. More experimental and pathologic evidence is therefore necessary to determine whether this flagellate may frequently invade the gallbladder or whether it obtains entrance only in the rôle of a secondary invader following an antecedent pathologic condition of the biliary tract.

There is no evidence of scientific value at present to support the theory of Barrow that *Giardia lamblia* is concerned in the etiology of arthritis deformans, certain forms of neurasthenia, melancholia with loss of weight and such symptoms as nausea, vomiting, belching of gas and epigastric pain and tenderness.

Book Reviews

Diätetik der Magen- und Darmkrankheiten von I. Boas, nebst Diätetik und Nachbehandlung bei Operationen am Magen-Darmkanal von G. Kelling. Ed. 2; enlarged and improved. Leipzig: Georg Thieme, 1926.

The introductory section of this work consists of an excellent statement of the principles of dietetics, with many practical hints as to their application. Simplicity is the keynote, and by the use of a few simple rules and the table given, caloric calculations can be rapidly and accurately made. Throughout the entire work not only the principles but also carefully worked out diet lists are given for almost every manifestation of gastro-intestinal disease. Unfortunately, these diets contain a high percentage of foods not available to the American public. Even their names have no English equivalents, and such lists would need complete revision to have any practical value outside of Germany. Another objection to the lists is the free use of innumerable proprietary foods.

One gets the impression, however, that dietetics is here given a much more important place in therapy than it really deserves. The twelve pages devoted to the dietary management of enteroptosis cannot but make one ask whether enteroptosis is a disease, and, if so, what possible influence diet can have. Again, in the comment on "nervous dyspepsia," one wonders whether the "nerves" are not being neglected while the dyspepsia is being overtreated.

In the latter section of the work dealing with surgical diseases, this fault is still more prominent. The importance of the diet, both before and after operation, is surely overemphasized. The more modern surgical point of view is, "The less interference with the patient's normal diet, the better." The administration of salts plus castor oil as a matter of routine before operation as here recommended cannot be too vigorously condemned. The restriction of food advised for the day before is too great, and the full diet is not restored soon enough to suit most surgeons today.

With the exception of such faults, which are common to all works in this field, the work is a valuable one. The principles underlying the disorders of nutrition are clearly and concisely stated, and an adequate scientific basis is given for the dietary control of these disorders. Finally, the practical means of applying these principles is made available to the general practitioner.

In the broader aspects of metabolism, means other than dietetic regulation are discussed. The water balance, acids and alkali relations, catharsis, enemas, etc., are considered as part of the problem. One of the best chapters in the book is that on extrabuccal nourishment.

Pernicious Anemia. By Frank Alexander Evans, M.D. Cloth. Pp. 170, with bibliography. Baltimore: Williams and Wilkins Company.

It is stated that the object of this book is to draw clinical pictures, reconsider treatment and discuss the more promising lines for study of the etiology of pernicious anemia. Certain considerations of the subject are taken from the field of orthodox discussion. In the chapter on classifications, the lines are more sharply drawn than usual, and there is a clear explanation of the basis on which the division is made.

Authorities are quoted in support of the statement that the number of cases of pernicious anemia is not increasing, and that the condition rarely, if ever, is found in people under 20 years of age. The danger of diagnosing pernicious anemia in the presence of a positive Wassermann reaction without first using thorough antisyphilitic treatment is emphasized. Other points as to incidence considered are: the few instances among negroes; its relatively frequent occur-

rence among Americans, Canadians, English, Irish and Scandinavians as compared with the peoples of Southern Europe; its infrequency in tropical Brazil, and the fact that heredity has not been shown to play any part in the matter.

With the exception of etiology, no other phase of this subject is more important for the practitioner than that of diagnosis. In the chapter dealing with this part of the subject, there is a good comparative discussion of the various factors that enter into the possible etiology, diagnosis and pathology of the disease. A comparison of the morphology of the blood as described here, with the descriptions found in the chapter "Clinical Description," leads to more or less the same kind of confusion that one finds in any analysis of the subject.

The subject of pernicious anemia is well presented in this book, which is written for practitioners, but one is inclined to inquire about the principle that should guide the practitioner in the selecting of his library. Monographs dealing with such subjects as pernicious anemia are justified only by some addition to the knowledge of the subject. The number of periodicals and books being published today makes it necessary for the practitioner who would be well informed as to progress in science to be careful of his time and money. It is on this basis that criticism is made of a new book on such a subject as this which makes no addition to what has already been written many times.

PRINCIPLES OF HUMAN PHYSIOLOGY. By E. H. STARLING. Fourth Edition. Price, $8. Pp. 1058. Philadelphia: Lea and Febiger, 1926.

The fourth edition of this excellent textbook differs little from the third which appeared in 1920. By omitting some material belonging more properly to chemistry and anatomy, the volume has been reduced from 1,298 to 1,058 pages.

The sequence in which the various topics are taken up remains unchanged, and it is not always satisfactory from the pedagogic standpoint. The author starts out well enough by a review of the material and the energetic bases of the body which the student should but probably does not know. After treating the most obvious and easily observable phenomena of movement and sensation, he discusses the central nervous system. He has added to the chapter on the cerebrum a brief but satisfactory exposition of Pawlow's work on the conditioned reflexes, but the subject of sleep is not even mentioned. Apparently Professor Starling is one of those who consider sleep unworthy of consideration by physiologists.

After the nervous system the sense organs are discussed, and their physiology receives adequate treatment. From this point on, the arrangement of the material seems to be highly illogical. Digestion and nutrition are considered before circulation and respiration, and it is hardly fair to the student to expect him to comprehend the phenomena of digestion and absorption without a knowledge of the circulation, and to understand metabolism without previous knowledge concerning the blood and respiration. There also seems to be some lack of proportion in the space allotted to the different subjects. Thus the chapter on the eye includes more than 80 pages (none too long, in our opinion), but only 19 pages are devoted to the chapter on the glands of internal secretion. Another shortcoming is the lack of references to the literature which are of value in enabling the curious student to obtain further information on subjects which attract his interest.

As a whole, however, the book is well written and is still one of the best texts on physiology at the present time.

GOITRE AND OTHER DISEASES OF THE THYROID GLAND. By ARNOLD JACKSON. New York: Paul B. Hoeber, 1926.

This work discusses a difficult and complicated subject in a manner that cannot be praised too highly. In all cases the data are reduced to the simplest possible terms, and in this form are of eminently practicable value. The

enormous literature has been sifted carefully and only the positive and proved points made available here for the general practitioner.

The first chapter deals with the thyroid gland, its anatomy and development, and concludes with an uncommonly concise statement of its function. This is followed by an equally clear exposition of what is known of its interrelation with other glands of internal secretion.

After the causes of goiter have been given, a classification is made. Here, again, simplicity is attained without sacrifice of truth. The small group of diseases of the thyroid given can be used to express clinical, histologic and physiologic facts with equal success.

The enormous increase of iodine hyperthyroidism since the modern prophylactic iodine medication is thoroughly reviewed. Workable rules are given for the administration of iodine in order to prevent this catastrophe, and comment is made on the whole matter of medical management.

Although the book is written from the surgical standpoint, the basic physiologic principles are not for a moment forgotten. Iodine has practically done away with the necessity for pole ligations. In the section on operative technic there are unfortunately included a number of reproductions of photographs that are poor. The illustrations in most cases are better but not especially clear.

Roentgen-ray treatment is given scant consideration.

THE HUMAN CEREBROSPINAL FLUID. AN INVESTIGATION OF THE MOST RECENT ADVANCES, AS REPORTED BY THE ASSOCIATION OF RESEARCH IN NERVOUS AND MENTAL DISEASE. THE PROCEEDINGS OF THE ASSOCIATION, NEW YORK, DEC. 29 AND 30, 1924. EDITORIAL BOARD: CHARLES L. DANA, M.D.; THOMAS K. DAVIS, M.D.; SMITH ELY JELLIFFE, M.D.; HENRY ALSOP RILEY, M.D.; FREDERICK TILNEY, M.D., and WALTER TIMME, M.D. Price, $10. Pp. 568, with 77 illustrations. New York: Paul B. Hoeber, 1926.

This is the fourth volume so far published by this active association, which has developed new methods in both organization and publication. There are thirty-nine contributors and, in addition, the volume contains much discussion, chiefly in the form of rigid cross-examination of the writers by the members of the commission to whom the papers are addressed. The following statement by the editorial committee in its preface, in view of the completeness and high quality of the volume, is a conservative estimate: "The committee believes that the volume represents the most up-to-date information on the subject, that it comprises material which up to now has been difficult of accessibility, and that the symposium that it embodies really furnishes the latest investigative results and the best current interpretation of both the physiological and the pathological aspects of the human cerebrospinal fluid."

There are thirty-one separate articles in the seven sections, which have the following titles: 1. The Normal Human Cerebrospinal Fluid; 2. Biological, Chemical and Physical Properties Under Normal and Pathological Conditions; 3. Pressure Studies of the Cerebrospinal Fluid; 4. The Diagnostic Replacement of the Cerebrospinal Fluid by Various Agents; 5. Changes in the Human Cerebrospinal Fluid in Connection with Diseases of the Central Nervous System; 6. The Reaction of the Human Cerebrospinal Fluid in Extraneural Diseases, and 7. The Treatment of Pathological Conditions Through the Cerebrospinal Fluid.

THE FINER DIAGNOSIS OF ACUTE BRAIN INVOLVEMENTS. INCLUSIVE OF SYPHILIS AND BRAIN INJURY. By J. VICTOR HABERMAN, A.B., M.D., S.M.D. (Berlin). Pp. 116. New York: Medical Journal and Record.

This is a monograph of 116 pages, nine of which contain bibliography. The acute conditions of the brain are considered from three points of view: the acute infection of the brain and its membranes, the reaction of the individual to brain injury or trauma and the acute vascular incidents in the brain. It

is essentially a compilation. A discussion of the spinal fluid occupies a large part of the text, but perhaps no more than is justifiable. In the chapter on brain injury the author warns against considering any symptoms as purely functional that are not due to organic disturbance of some variety. He does not give any suggestion concerning diagnosis of functional conditions from organic, but, considering the title, he is perhaps right in this stand. The paragraphs on late aneurysm are interesting though no allowance is made for the possibility of coincidence. This is a useful monograph for the student and general practitioner.

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